REVIEWS

Asthma Exacerbations: The Genes Behind the Scenes

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, USA
[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

■ **Abstract**

The clinical and socioeconomic burden of asthma exacerbations (AEs) constitutes a major public health problem. In the last 4 years, there has been an increase in ethnic diversity in candidate-gene and genome-wide association studies of AEs, which in the latter case led to the identification of novel genes and underlying pathobiological processes. Pharmacogenomics, admixture mapping analyses, and the combination of multiple "omics" layers have helped to prioritize genomic regions of interest and/or facilitated our understanding of the functional consequences of genetic variation. Nevertheless, the field still lags behind the genomics of asthma, where a vast compendium of genetic approaches has been used (eg, gene–environment interactions, next-generation sequencing, and polygenic risk scores). Furthermore, the roles of the DNA methylome and histone modifications in AEs have received little attention, and microRNA findings remain to be validated in independent studies. Likewise, the most recent transcriptomic studies highlight the importance of the host–airway microbiome interaction in the modulation of risk of AEs. Leveraging -omics and deep-phenotyping data from subtypes or homogenous subgroups of patients will be crucial if we are to overcome the inherent heterogeneity of AEs, boost the identification of potential therapeutic targets, and implement precision medicine approaches to AEs in clinical practice.

Key words: Asthma exacerbations. Genomics. Epigenetics. Transcriptomics.

■ **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 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 ha 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.

■ **Definitions**

- Candidate-gene association study: Statistical approach that interrogates the association between genetic variation and a trait of interest and analyzes genomic regions selected based on a biological hypothesis.
- Genome-wide association study (GWAS): Agnostic scan of genetic variation across the genome to establish an 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 (eg, environmental or genetic factors) in a phenotype under study.
- Admixture mapping: Gene mapping approach that investigates whether chromosomal ancestry (local ancestry) is associated with a trait of interest, thus enabling the detection of genomic regions harboring genetic variants that exhibit differences in ancestry.
- Next-generation sequencing (NGS): High-throughput technology that makes it possible to determine 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 makes it possible to detect genetic variation in the genomic protein-coding regions (exons).
- Whole-genome sequencing (WGS): Next-generation approach that determines the DNA sequence in the entire genome.
- Epigenome-wide association studies (EWAS): Agnostic scan of epigenetic markers, usually DNA methylation, across the genome to determine association with a trait of interest.
- Transcriptome-wide association studies (TWAS): Agnostic gene-based scan of gene expression across the whole genome to determine association with a trait of interest.
- Proteome-wide association studies (PWAS): Agnostic scan of protein expression to determine association with a trait of interest.
- Metabolome-wide association studies (MWAS): Agnostic scan of metabolite levels to determine 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), and metabolite levels (metabolic quantitative trait locus, mQTL).
- Expression quantitative trait methylation (eQTM): Position of the DNA sequence where methylation levels are associated with gene expression levels.

Introduction

Asthma exacerbations (AEs) are episodes of worsening symptoms requiring a change in treatment. AEs 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 corticosteroids (oral, intramuscular, or intravenous). However, this definition should be used with caution because it often relies on an individual's self-report and does not consider other clinical or physiological parameters underlying 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 [3]. In the United States of America (USA), there are approximately 170 000 asthma-related hospitalizations, 1.8 million ED visits, and 4000 asthma-related deaths per annum. In fact, yearly asthma health care expenditure amounts to £1.1 billion in the United Kingdom [4] and $50.3 billion in the USA [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 decline in lung function [9-13], infants with reduced airway caliber 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 remodeling, 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 previous year [18-20], thus, highlighting the need to investigate the key roles of genetic factors and/or early-life determinants on these events. In addition, identifying clinically relevant biomarkers or predictors of AEs plays a key role in reducing and preventing them. AEs are likely due to the complex interplay of genetic, environmental, and behavioral factors [18,21-23]. In fact, risk factors for AEs include allergens, air pollution, exposure to tobacco smoke, viral infections, psychological stress, poor adherence to treatment, obesity, and genetic factors [18].

Ethnic differences in the patterns of AEs are evidenced worldwide. In the USA, AE rates are higher among African Americans and Puerto Ricans [24-28], while in Europe, they are higher in southern European countries [29]. African Americans are also more likely to have longer lengths of stay in intensive care units than Europeans [30]. In fact, African ancestry has been associated with AEs among African Americans [31] and other individuals of African descent in the USA [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 between African ancestry and readmissions for asthma in African Americans may be mediated by disease management and socioeconomic factors [36].

Herrera-Luis et al [16] provided a detailed description of genetic association studies of AE published until November 15, 2018. Gautam et al [37] reviewed the transcriptomics of asthma susceptibility, disease severity, and AEs prior to 2022, although no extensive summary of epigenetic studies of AEs has been published to date. 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 October 1, 2022 and review epigenetic aspects of AEs.

Literature Mining

Literature mining of genomic, epigenetic, and transcriptomic studies of AEs was conducted in PubMed [38] by applying the following search terms: (Transcriptomics [Title/Abstract] OR Candidate gene [Title/Abstract] OR polymorphism [Title/Abstract] OR SNP [Title/Abstract]
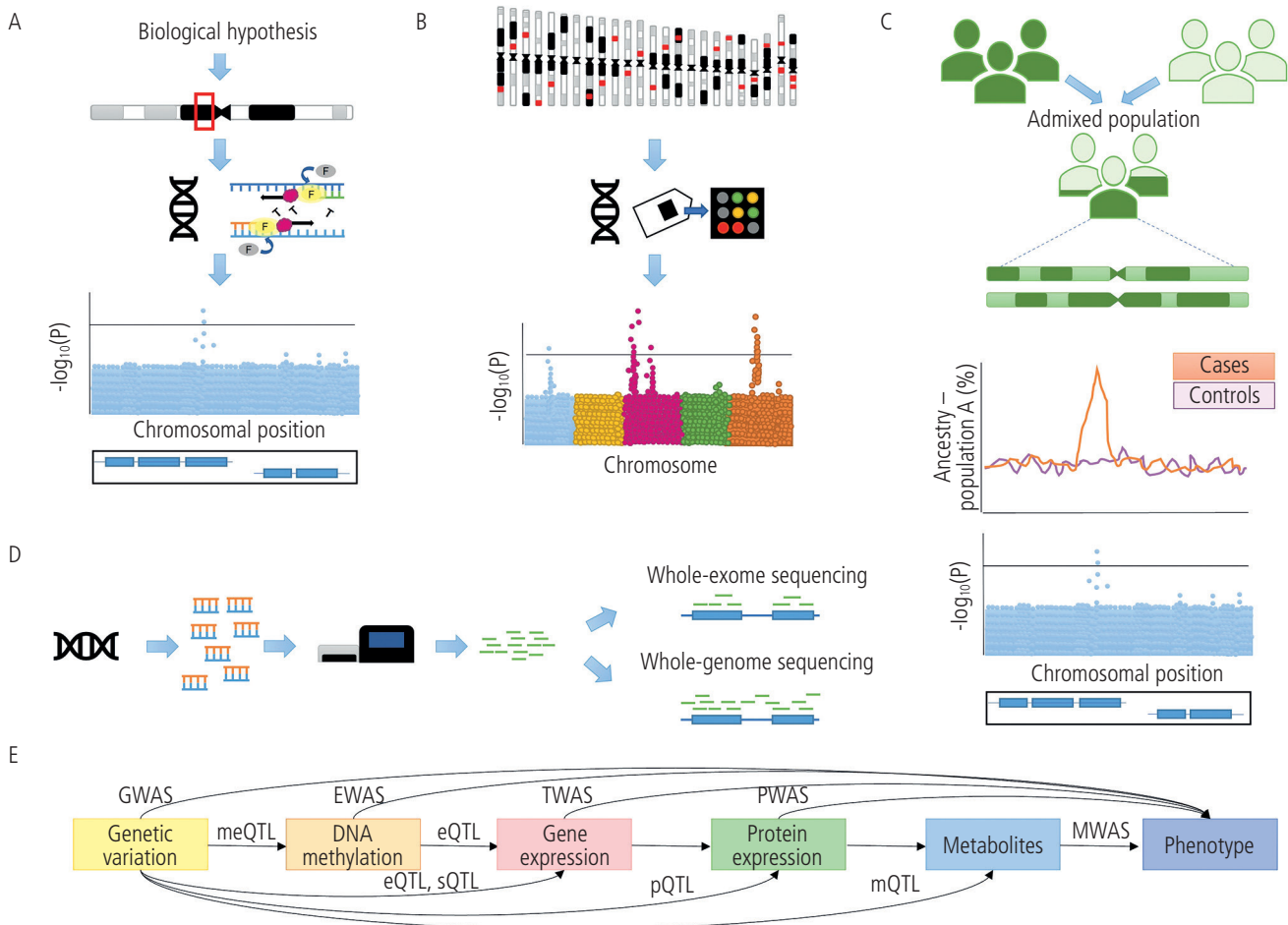
Figure. A, Candidate-gene association study. A biological hypothesis is used to prioritize genomic regions that will be genotyped, and genetic variants within the regions will be tested for association with the trait of interest. B, Genome-wide association study (GWAS). Genetic variation is profiled 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 focuses on genomic protein-coding regions (exons), whole-genome sequencing determines genetic variation in any part of the genome. E, Combination of different -omics 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, effects can be observed with regulatory genetic variants, for example, 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). In addition, methylation levels at a specific chromosomal position may regulate gene expression levels (expression quantitative trait methylation [eQTM]).

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 the following: (*1*) reviews, editorials, or opinion articles; (*2*) findings in animals or cell lines; and (*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, A). However, candidate-gene association studies are hampered by nonreproducibility 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 assessment of genetic variation across the genome for association with a trait. These hypothesis-free strategies can uncover novel pathogenic mechanisms, potentially leading to new therapeutic targets [40] (Figure, B). 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 variations (<1% minor allele frequency) may be implicated in the pathophysiology of AEs, whole-genome or exome association studies have yet to be conducted for AEs (Figure, C).

In populations resulting from the admixture of 2 or more ancestral populations, admixture mapping analysis can be an alternative strategy that avoids the high penalty of statistical significance in GWASs, particularly in genetically complex populations, which are 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, D). 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 toward uncovering variants with modest effect sizes (ie, candidate gene studies) or located in noncoding regions of the genome (ie, 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 -omics layers (Figure, E) has become easier, given the availability of multiple free tools online (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 interleukin 33 (*IL33*) [50],

vitamin D receptor (*VDR*) [54], and *SERPINE1* encoding 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 ability to predict ED management failure compared with the clinical model alone (area under the curve [AUC]: 0.82 vs 0.79, P=.0004) [50]. Moreover, an expression quantitative trait loci analysis of respiratory syncytial virus–related genes narrowed down the modulatory effect of respiratory syncytial virus infection on a *CEACAM3* locus for AEs [53]. Likewise, a candidate-gene association study of 6 genomic regions harboring 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 in adults [64] and whose effects may be intensified by early-life and passive tobacco smoke exposure [65,66]. As expected for the most consistently replicated signal of asthma across populations, genetic variation and gene-by-environment interactions for chromosome 17q12-21 have been investigated in relation to AEs [1,67]. More recently, the effect of the *GSDMB* rs7216389 SNP 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 gene-by-environment evidence on asthma susceptibility [67].

Two recent studies of Korean individuals 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 that acts as an inhibitor of type I interferon signaling, 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 corticosteroid treatment in various airway cell types [62].

In the period reviewed, 4 candidate gene studies explored susceptibility variants for response to inhaled corticosteroids (ICS) [60,61,63,70], long-acting ß2-agonists [55], and montelukast [58] using AEs as a clinical endpoint. Four of them assessed asthma-related genes, as follows: *IL1RL1* [60] and *CRHR1* [61] for response to ICS, *ADRB2* [55] for response to long-acting ß2 agonists, and *LTA4H* [58] for response to montelukast. The other 2 combined or integrated multiple omics to prioritize candidate genes [63,70]. Hernandez-Pacheco et al [57] identified a member of the family of latent-transforming growth factor ß–binding proteins (*LTPB1*) as differentially expressed after exposure to corticosteroids in several transcriptomic datasets from airway smooth muscle cells and peripheral blood mononuclear cells. Within *LTBP1*, 2 polymorphisms associated with AEs exerted ethnicity-specific effects [70]. Kan et al [63] leveraged a previous GWAS of change in forced expiratory volume in 1 second (FEV$_1$) after ICS treatment ($P<1\times10^{-4}$), chromatin immunoprecipitation

Table 1. Main Findings and Characteristics of Candidate-Gene Studies of Asthma Exacerbations Conducted From November 15, 2018 to October 1, 2022

rsID (Gene)	Participants	Phenotype	EA/EG	Effect size (95%CI) or (SE)	P Value	PMID [reference]
rs295137 (SPATS2L) rs7037276 (IL33) rs1342326 (IL33)	491 European children with moderate-to-severe asthma presenting to the ED	Hosp/active asthma management ≥8 h in ED after OCS/return visit within 72 h for one-off events after presenting to the ED	T T C	OR, 1.77 (1.17-2.68) OR, 0.55 (0.33-0.90) OR, 0.52 (0.32-0.86)	.006 .02 .01	30644648 [50]
rs16986718 (NLRP4)	1-y longitudinal study of 1454 Korean individuals with asthma, including 955 never-smokers	Number of ED visits/Hosp/OCS/rescue bronchodilator/increase in asthma medication ≥2 exacerbation events vs one/none	G	Increased annual exacerbation episodes OR, 2.56 (NA) NA	.001 6.7×10^{-5} .014	30526007 [51]
rs1799768 (SERPINE1)	265 individuals (48% European, 43% African/African American) with poorly controlled asthma enrolled in a randomized clinical trial of soy isoflavones	OCS Soy isoflavones intake×SNP on OCS Number of OCS events/person-year	4G4G/4G5G vs 5G/5G	IRR, 2.57 (1.09-6.07) NA RR, 0.28 (0.12-0.59)	.031 .005 <.001	30707970 [52]
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 wk. Replication: Asthma-related limitation of activity/wheezing-induced nocturnal awakenings at least once a month in the last 2 mo RSV x SNP on exacerbation.	CT/TT vs CC	$OR_{Discovery}$, 2.58 (1.65-4.03) $OR_{Replication}$ 1.53 (1.03-2.31) NA	3.12×10^{-5}; .035 .03	32606071 [53]
rs1544410 (VDR) rs2228570 (VDR)	657 Australian children (64.2% European) presenting to the ED with acute asthma/wheezing/ bronchiolitis	Exacerbation severity Z-scores Exacerbation severity Z-scores Lifetime Hosp for acute respiratory illnesses	TT vs CC AA vs GG AG vs GG	Increased severity scores Increased severity scores Increased severity scores	.005 .001 .011	32380236 [54]
ADRB2 variants	832 children with asthma	Hosp/ED visits/OCS in the last 6-12 mo despite ICS plus LABA use	Arg16/Gln27 vs Gly16/Glu27 Arg16/Gln27 vs Gly16/Gln27	1.40 (1.05-1.87) 1.43 (1.05-1.94)	.022 .023	34128573 [55]
rs67622929 (DNASE1L3)	Discovery: 1002 African American individuals with asthma. Replication: 2181 Hispanic/Latino children with asthma	Hosp/ED visits/OCS in the last 12 mo	C	$OR_{Discovery}$, 1.48 (1.18-1.87) $OR_{Replication}$ 1.18 (1.01-1.37)	7.9×10^{-4}; .03	33035569 [56]
rs11681246 (LTBP1) rs76390075 (LTBP1)	2681 European children 1347 Hispanic/Latino or African American children with asthma	Hosp/ED visits/OCS in the last 6-12 mo despite ICS use	G C	OR, 0.72 (0.63-0.83) OR, 0.40 (0.26-0.63)	3.28×10^{-6} 6.76×10-5	32786158 [57]

(continued)

Table 1. Main Findings and Characteristics of Candidate-Gene Studies of Asthma Exacerbations Conducted From November 15, 2018 to October 1, 2022 *(continuation)*

rsID (Gene)	Participants	Phenotype	EA/EG	Effect size (95%CI) or (SE)	P Value	PMID [reference]
rs2660845 (*LT44H*)	Patients with asthma. Discovery: 523 European individuals with early-onset asthma; R_1: 2514 European individuals with early-onset asthma; R_2: 486 Hispanic/Latino children; R_3: 71 African American children	Hosp/ED visits/OCS in the last 6-12 mo 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)	.041; R1: .833; R2: .788; R3: .019	34550981 [58]
rs2517955 (*PGAP3*); rs1031458 (*GSDMB*); rs3902920 (*GSDMB*)	3-y longitudinal study of 273 non-Hispanic White adolescents and adults with asthma	Number of asthma-related ED visits/Hosp in 3 y	C; G; T	β, 1.05 (NA); β, −0.77 (NA); β, −0.88 (NA)	.0034; .028; .012	32795586 [59]
rs13431828 (*IL1RL1*)	2412 European, Hispanic/Latino, or African American children	Hosp/ED visits in the last 6-12 mo despite ICS use	C	OR, 1.32 (1.08-1.62); OR, 1.31 (1.07-1.59)	.02; .02	31755552 [60]
rs242941 (*CRHR1*); rs1134481 (*TBXT*); rs37973 (*GLCCI1*)	European adult patients with asthma ($n_{Discovery}$: 597; $n_{Replication}$: 9842)	Hosp/ED visits/OCS despite ICS use	A; T; G	$RR_{Discovery}$, 6.11 (NA); $RR_{Replication}$, 1.16 (NA); $RR_{Discovery}$, 0.36 (NA); $RR_{Replication}$, 1.02 (NA); $RR_{Discovery}$, 1.88 (NA); $RR_{Replication}$, 0.82 (NA)	<.005; .004; <.005; .563; <.005; <.005	33428814 [61]
rs1384006 (*OXSR1*)	1-y longitudinal study of 1454 Korean individuals with asthma, including 955 never-smokers	Number of ED visits/Hosp/OCS/rescue bronchodilator/increase of asthma medication ≥2 exacerbation events vs one/none	C	Increased annual exacerbation episodes; OR, 0.36 (0.18-0.72)	.004; .004	34983467 [62]
rs9665961 (*BIRC3*)[a]	5710 European adults, 166 European children, 854 Hispanic/Latino children and 493 African American children with asthma	Hosp/ED visits/OCS in the last 6-12 mo despite ICS use/8% decrease in FEV_1 in patients after 6 wk of ICS therapy	A	OR, 0.81 (NA)	3.77×10^{-4}	34971648 [63]

Abbreviations: ß, regression coefficient; EA/EG, effect allele/genotype; ED, emergency department; FEV_1, forced expiratory volume in the first second; Hosp, hospitalization; ICS, inhaled corticosteroids; IRR, incidence risk ratio; LABA, long-acting ß2-agonists; NA, not available; OCS, oral corticosteroid use; OR, odds ratio; RR, relative risk; Rn, replication study (number ₙ); RSV, respiratory syncytial virus; SE, standard error of the ß coefficient; SNP, single-nucleotide polymorphism.

[a]A total of 35 SNPs in linkage disequilibrium ($r^2 \geq 0.8$) were significantly associated with asthma exacerbations 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 multiancestry meta-analysis.

sequencing, and transcriptomics to develop a multiomics integrative score that prioritized a locus harboring 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 Hispanic/Latino, African American, and European individuals.

GWAS

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

Most genetic association studies of AEs have been conducted in Europeans [16], although 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 Hispanic/Latino children (n=4010) uncovered a significant genome-wide association in *LINC03033*, a long noncoding RNA (lncRNA) that participates in myofibroblast differentiation and airway remodeling [72]. The risk allele for AEs was associated with higher DNA methylation (DNAm) levels in *LINC03033* in nasal epithelium. This, in turn, was associated with higher expression of *KCNJ2-AS1* [72], which is also overexpressed in atopic asthma [84]. Another recent GWAS compared asthma cases with AEs to controls without asthma to overcome the reduced statistical power resulting from the complex genetic structure in recently admixed populations; the objective of the study was to identify genetic signals for asthma in Hispanic/Latino and African American children with AEs [73]. A genome-wide significant locus near lncRNA *LINC01913* was associated with asthma with severe exacerbations, possibly through expression of *LINC01913* 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, which codes for a regulator of proteins of the nervous system, was associated with the annual number of AEs in Koreans [75]. More recently, a multiancestry meta-analysis of GWAS of AEs identified 2 suggestive variants associated with blood DNAm or expression levels of genes participating in inflammation and host defense (*VCAM1*, *EXTL2*, and *PANK1*) [76].

Pharmacogenomic GWAS of AEs have identified susceptibility variants for response to ICS [1,77,80,82,85] and LABAs [79]. Genomic regions harboring 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]), and the Wingless/integrase 1 signaling (*WNT5A*) pathway [80]. Moreover, 2 studies considered AEs despite ICS use as a secondary

outcome to validate genetic associations for response to ICS 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 exerted specific effects 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 diagnostic codes, and a genome-wide signal for oral corticosteroid (OCS) use near *PTCHD4*, which encodes a regulator of hedgehog signaling previously associated with airway disease [82]. Furthermore, a genome-wide interaction study of the association between age and AEs despite ICS use found significant genome-wide signals in genes implicated in angiogenesis, lung function, and chronic obstructive pulmonary disease (COPD) (*THSD4*), inflammatory and immune processes, and response to corticosteroids (*HIVEP2*) [83]. Moreover, the only multiancestry meta-analysis of GWAS of AEs despite treatment with LABAs revealed suggestive associations within genes previously implicated in lung function (*TBX3* [88]) and response to short-acting ß2-agonists (*EPHA7* [89]).

As previously indicated, some studies aimed to shed light on 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 nonsmokers 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 signaling, antigen cross-presentation, and vesicular transport [82]. Among European children treated with ICS, genetic variants associated with AEs were enriched in asthma-related genes that showed differential expression when exposed to trichostatin A [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 the need for further research into the therapeutic potential of trichostatin A in asthma.

Admixture mapping

Admixture mapping studies have identified genetic variants associated with asthma, IgE levels, bronchodilator response, and lung function [42,94], although only 2 admixture studies of AEs have been published (Table 3). The only admixture mapping of AEs independent of treatment conducted in Hispanic/Latino individuals 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–Hispanic/Latino individuals. The risk allele

Table 2. Main Findings and Characteristics of Genome-Wide Approaches to Study the Genetic Factors Involved in Asthma Exacerbations Conducted From November 15, 2018 to October 1, 2022

Type of study	rsID (Gene)	Participants	Phenotype	EA	Effect size (95%CI) or (SE)	P Value	PMID [reference]
GWAS	rs56151658 (HLA-DQB1)	Discovery: 34 167 White British adults with asthma Replication: 2645 Hispanic/Latino children with asthma	ED/Hosp/OCS	A	OR$_{Discovery}$: 1.36 (1.22-1.52) OR$_{Replication}$: 1.19 (0.99-1.42)[a,b]	3.11×10^{-8} 5×10^{-3a}	32890573 [71]
GWAS	rs2253681 (LINC03033)	4010 Hispanic/Latino adolescents with asthma	ED/Hosp/OCS	A	OR: 1.55 (1.34-1.79)	6.3×10^{-9}	33093117 [72]
GWAS	rs4952375 (LINC01913)	Children with asthma. Discovery: 3310 Hispanic/Latino; replication: 1043 African American	ED/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) rs696733010 (CDHR3) rs107163018 (HLA-DQA1) rs34093366 (IL33) rs134232666 (IL33) rs1018962918 (IL1RL1) rs104382818 (WDR36) rs2054118 (IL13) rs281379 (FUT2/MAMSTR)	Discovery: 2866 European children experiencing severe AE between ages 2 and 6 years, and 65 415 nonasthmatic controls. Replication: 1118 children	Discovery: Asthma with Hosp; Replication: Asthma	T A C G C C C A G	OR: 1.65 (1.56-1.75) OR: 1.41 (1.32-1.51) OR: 1.25 (1.18-1.32) OR: 1.37 (1.26-1.49) OR: 1.31 (1.22-1.40) OR: 1.40 (1.27-1.54) OR: 1.20 (1.14-1.27) OR: 1.21 (1.13-1.29) OR$_{Discovery}$: 1.18 (1.11-1.25) OR$_{Replication}$: 1.43 (1.16-1.79)	1.6×10^{-68} 2.1×10^{-23} 8.0×10^{-14} 1.6×10^{-13} 1.7×10^{-13} 7.7×10^{-12} 1.0×10^{-10} 1.0×10^{-8} 2.6×10^{-9}; 1.1×10^{-3}	33328473 [74]
GWAS	rs10519519 (MYT1L)	1-year longitudinal study of 20 nonsmoking 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 (4989 patients with asthma): 53.1% European, 23.2% Hispanic/Latino, 13.3% Singaporean Chinese, and 10.3% African American. Replication: 36 477 European and 1078 non-European asthma patients	ACC/ED/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 American. Replication: 1697 European	ED/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}	30697902 [77]
PGWAS (ICS)	rs5995653 (APOBEC3B/APOBEC3C)	Children with asthma. Discovery: 854 Hispanic/Latino and 493 African American. Replication: 1697 European	ED/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}	
	rs62081416[a] (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 American. Replication: African American (nR1=803 and nR2=563) and Latino (nR3=1461)	Discovery: SNPxICS adherence on change in ACT score over 6 wk of ICS treatment. Replication 1: SNPxICS adherence on time to ED/Hosp/OCS. Replication 2-3: SNPxICS use on ED/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]

(continued)

Table 2. Main Findings and Characteristics of Genome-Wide Approaches to Study the Genetic Factors Involved in Asthma Exacerbations Conducted From November 15, 2018 to October 1, 2022 (*continuation*)

Type of study	rsID (Gene)	Participants	Phenotype	EA	Effect size	P Value	PMID
PGWAS (LABA)	rs1947048 (*EPHA7*)	1425 children and young adults with asthma (23% Hispanic/Latino, 10.4% African American, 32.5 Singaporean Chinese)	ED/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: 2681 European. Replication 1: 538 European. Replication 2: 854 Hispanic/Latino, 493 African American, 426 Singaporean Chinese	ED/Hosp/OCS/SA despite ICS use	C	$OR_{Discovery}$: 1.50 (0.93-2.43) OR_{R1}: 1.83	4.22×10^{-6}; R_1; 0.01; R_2: NS (1.16-2.90)	33303529 [80]
PGWAS (ICS)	rs1166980 (*ROBO2*)	Children with asthma. Discovery: 166 European. Replication 1: 2681 European. Replication 2: 854 Hispanic/Latino, 493 African American	Discovery: ≥8% in FEV$_1$ after 6 wk of ICS treatment Replication: ED/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[c] (*ROBO2*)	Discovery: 2681 European	ED/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 ($n_{Discovery}$= 5710; $n_{Replication}$=1141)	OCS despite ICS use	G	$OR_{Discovery}$: 1.73 (1.39-2.16) $OR_{Replication}$: 1.48 (0.75-2.90)[c]	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)[c]	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)[c]	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)[c]	5.28×10^{-7}; 3.56×10^{-3}	
PGWIS (Age; ICS)	rs34631960 (*THSD4*)	1321 European adul and	SNPxAge use on children with asthma ED/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}	

Abbreviations: ACC, acute asthma care; ACT, Asthma Control Test; Coef, interaction coefficient estimate; EA, effect allele; ED, emergency department; FEV$_1$, forced expiratory volume in the first second; GWAS, genome-wide association study; Hosp, hospitalizations; ICS, inhaled corticosteroids; LABA, long-acting ß-agonists; OCS, oral corticosteroid use; NA, not available; NS, nonsignificant; 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; SNP, single-nucleotide polymorphism.
[a]rs56151658 was not available in Hispanic/Latino individuals. The results for the most significant proxy in Latinos (r^2=0.71) are shown (rs9275356).
[b]Effect size from the largest replication cohort is shown.
[c]The genetic variant was identified using a candidate-gene approach using the GWAS summary statistics.

of rs1144986 was associated with altered *DPYSL3* DNAm levels and lower gene expression of *SCGB3A2* in blood. While *DPYSL3* may be involved in airway remodeling, SCGB3A2 is an upstream regulator of TGFβ-mediated antifibrotic processes in the lung [92].

Another study investigated the association between local ancestry and response to different step-up regimens including ICS in 516 individuals of African descent with asthma [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 who transitioned from low-dose ICS to the quintuple dose of ICS than in those who received 100 µg fluticasone

Table 3. Main Findings and Characteristics of the Admixture Mapping Studies of Asthma Exacerbations Conducted From November 15, 2018 to October 1, 2022

rsID (Gene) Chromosomal band	Participants	Phenotype	EA	OR (95%CI)	P Value	PMID [reference]
rs1144986 (*C5orf46*) 5q32	Patients with asthma. Discovery: 625 Mexican American. R1: 1124 Puerto Rican R2: 1001 African American, 1250 Singaporean, and 941 European.	ED/Hosp/OCS	G	Discovery: 0.43 (0.28-0.66) R1: 0.79 (0.62-1.00)	9.45×10^{-5}; 4.94×10^{-2}; NS	36180068 [92]
rs5752429 (*TPST2*) 2q12.1	Discovery: 266 adolescents/adults of African descent Replication: 222 African American	Discovery: Better response to 5xICS vs 2.5xICS Replication: ED/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 Replication: 379 African American	Discovery: Better response to 5xICS vs 100 µg fluticasone plus salmeterol Replication: ED/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	

Abbreviations: EA, effect allele; ED, emergency department; Hosp, hospitalisations; ICS, inhaled corticosteroids; NS, nonsignificant; OCS, oral corticosteroids.

Table 4. Main Findings of the Studies of DNAm in Asthma Exacerbations

Biological sample	Participants	Phenotype	CpG	Gene/Nearest Gene	Regression coefficient (95%CI)	P Value	PMID [reference]
Cord blood	303 children recruited by a birth cohort in Manchester (UK)	Asthma-related hospitalizations or ED after the first year of life Asthma/wheeze-related hospitalization after the first year of life	Promoter site 1	*IL2*	1.07 (1.01,1.14) 1.12 (1.04,1.20)	.03 .002	23414538 [98]
Blood	394 children treated with ICS (57.4% European, 42.6% Hispanic /Latino)	Asthma-related hospitalizations or ED in the past year despite ICS use OCS use in the past year despite ICS use.	cg00066816 cg00557354 cg04256470 cg09495977 cg12333095 cg13818573 cg21589280 cg03080985 cg04330449 cg05307923 cg08724517 cg11665562 cg14269514 cg24322623	*IL12B* *ARHGEF7* *CORT, CENPS* *HTRA3* *ANKRD13A* *C1QL1* *DDAH1* *SH3BGRL2* *NEUROG1* *ADARB2* *MAP9* *PSMC1* *OAZ3, MRPL9* *MYOD1*	−3.10 (NA) −3.49 (NA) 3.62 (NA) −2.42 (NA) −3.48 (NA) −3.59 (NA) −3.06 (NA) −3.07 (NA) −2.64 (NA) −2.57 (NA) 2.95 (NA) −3.25 (NA) −3.11 (NA) −2.96 (NA)	.002 .001 <.001 .017 .001 <.001 .003 .003 .009 .011 .004 .001 .002 .004	31187518 [99]

Abbreviations: ED, emergency department visits; ICS, inhaled corticosteroids; NA, not available OCS; oral corticosteroid bursts.

plus salmeterol. Moreover, African ancestry at chromosome 22q12.1 was associated with better responsiveness in adults who transitioned from low-dose ICS to the quintuple dose of ICS than in those who received 2.5 times the ICS dose. Analysis of genetic variants within these regions revealed 1 SNP that was consistently replicated for association with AEs in African Americans treated with ICS [93].

Epigenetics

The 3 main epigenetic mechanisms that act synergistically to regulate gene expression are DNAm, histone modifications,

and noncoding 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. However, CpG-rich regions, known as CpG

Table 5. Main Findings and Characteristics of miRNA Studies in the Context of Asthma Exacerbations

Biological sample	miRNA profiling	Participants	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 severity of adverse event	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	Participants with (n=59) and without asthma (n=11) recruited in the United States	Lifetime and past 12 mo 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 mo 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-wk 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	Participants 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/T$_H$17 signalling and endoplasmic reticulum stress.	32255668 [109]
Whole blood	Small-RNA sequencing	Costa Rican children with asthma (n$_{FE}$=183; n$_{IF}$=168) from GARCS	≥3 events of asthma-related ED/AC visits and/or hospitalizations in the last 12 mo (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; ED, emergency department; 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; T$_H$17, T-helper type-17 cells; TLR, toll-like receptor; WGCNA, weighted gene co-expression network analysis.

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 1 targeted DNAm study of AEs [98] and 1 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. Furthermore, Wang et al [99] conducted a multiancestry EWAS meta-analysis of peripheral blood CpG markers and AEs despite treatment with ICS. Hypomethylation of cg00066816 upstream of *IL12B*, which encodes for a subunit of the heterodimeric IL-12, a proinflammatory cytokine involved in T_H1 and T_H17 signaling [100], was nominally associated with the absence of asthma-related ED visits or hospitalizations in the previous year in children taking ICS. In a secondary analysis, 13 CpGs were differentially methylated in patients who received OCS bursts in the previous year despite ICS use. Although functional effects of DNAm on blood gene expression were explored, the CpG-gene pairs were not consistently replicated across studies [99].

miRNAs

miRNAs are posttranscriptional regulators that exert their effects by binding to the 3′ untranslated regions of mRNAs, leading to mRNA deadenylation and subsequent degradation. These small noncoding 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, 7 studies have addressed the role of miRNAs in AEs, including 3 studies in blood, 3 in serum, and 1 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 applied a systems biology approach. Specifically, Gomez et al [109] conducted a weighted gene coexpression network analysis (WGCNA) of miRNA and mRNA expression levels in induced sputum from 61 individuals 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/T_H17 signaling pathway and endoplasmic reticulum stress. One of the miRNAs associated with high sputum neutrophil counts in response to ozone exposure, hsa-miR-223-3p, acted as a regulator of both mRNA modules [109].

Midyat et al [104] reported that 10 of 739 tested miRNAs were differentially expressed according to the severity of asthma and AEs in children. Another study found that miR-1 was downregulated in acute-stage asthma and predicted asthma attacks with an AUC of 0.90, which was significantly higher than the AUC from asthma-related cytokines (eg, IL-4 or IL-5) ($P<.05$) [105]. Analysis of animal models and primary human endothelial cells has shown miR-1 to be implicated in the regulation of airway eosinophilia through the inhibition of eosinophils binding to the endothelium by promoting RNA-induced gene silencing of eosinophil trafficking genes [106].

In a 6-week longitudinal study, expression of 3 of 7 circulating miRNAs tested (miRNA-126a, miRNA-16, and miRNA-21) were significantly lower during an AE episode than at a follow-up visit [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 ppb. miRNA-126a and miRNA-21 are both considered promoters of T_H2-mediated allergic inflammation [101,111], and miRNA-21 is a systemic oxidative stress marker that is dysregulated in the airways and/or blood in atopic dermatitis and allergic asthma [101].

In an analysis of patients who experienced frequent exacerbations and infrequent/no exacerbations, 20 of 649 tested blood miRNAs were differentially expressed by individuals with 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 the PI3K-Akt and MAPK signaling pathways [110], which are relevant in T_H2 inflammation and asthma pathogenesis [102].

Table 6. Main Findings and Characteristics of Transcriptomic Studies of Asthma Exacerbations Conducted in 2022 (up to October 1, 2022)

Biological sample	RNA profiling	Participants	Phenotype	Main findings	PMID [reference]
Nasal blow	RNA-seq (NextSeq 500 platform)	208 children with asthma from the 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	Genome U133 Plus 2.0 Array (Affymetrix).	317 participants with severe asthma from Europe	≥2 events of systemic corticosteroids use vs FE <2 events 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.

Only 1 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]. The univariate logistic regression models showed 12 of the 125 tested serum miRNAs to be 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 than clinical score alone (AUC, 0.81 vs 0.67) [107]. Of note, in individuals with asthma, serum miR-146b-5b and miR-206 levels have been associated with asthma and COPD [103], as well as with baseline FEV_1/FVC [112].

Transcriptomics

Studies of transcriptomics and AEs prior to 2022 were recently reviewed by Gautam et al [37]. The authors identified distinct AE-related gene expression signatures implicated in innate and adaptative immunity and in viral and nonviral exacerbations and revealed genes implicated in frequent exacerbations (*TNFR2*) and in AEs triggered by cold (genes implicated in the *SMAD3* signaling pathways). The only single-cell RNA-sequencing study conducted in the context of AEs highlighted the implication of several cytokines and intracellular transduction regulators in multiple cell types in these asthma outcomes [113].

Two transcriptomic studies of AEs were published during the period reviewed (Table 6). One focused on the effect of the interaction between 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]. The other aimed to understand the pathophysiological factors underlying frequent exacerbations using transcriptomic data from bronchial biopsies. *CEACAM5*, which encodes a cell surface glycoprotein upregulated by interferon-γ [115], was the only transcript differentially expressed in individuals with frequent exacerbations compared to those with infrequent exacerbations. However, no differential expression was found when individuals 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 individuals with frequent exacerbations showed higher expression of those signatures than individuals with persistent frequent exacerbations [116].

Conclusion and Future Directions

AEs constitute a major burden for individuals with asthma and their caregivers, health care systems, and society as a whole. Although preventing AEs is key in clinical practice, stratification of patients with AEs by risk is challenging owing to the inherent heterogeneity of the biological mechanisms underlying these events. Nevertheless, -omics 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 in terms of comparison with -omics findings in other respiratory traits, such as asthma [37] and COPD [117-119].

Given the heterogeneity of AEs, specific phenotyping approaches may be 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. These would enable the characterization of gene–environment interactions, which are 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 identification [121]. Interestingly, differences in the definition of AEs, triggers, and clinical characteristics of individuals with asthma may have reduced statistical power in several GWAS [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 risk burden score or polygenic risk score (PRS) for AEs is not feasible without additional risk stratification that also considers clinical and environmental parameters. Recently, a multiancestral PRS for asthma developed using lasso [123] or Bayesian regression [124] captured the risk of asthma, although other studies have failed to achieve this [125,126]. A PRS incorporating DNAm or gene expression data may better capture environmental influences and improve risk stratification [127]. The extent to which methylation risk scores or transcriptome risk scores may contribute to risk prediction remains to be determined, although 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], although only 1 GWAS of the annual number of exacerbations has been conducted [75], and no studies have assessed the temporal distance between events and/or the time to first exacerbation. Moreover, although bioinformatics 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 individuals with asthma, across several asthma-relevant tissues, or from diverse ethnic backgrounds. In this sense, experimental studies are required if we are to understand the biological role of the genes identified and establish their prognostic value with the aim of adequately implementing precision medicine in patient risk stratification and prioritizing potential therapeutic targets.

The role of rare variants in AEs has been poorly investigated, even though 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 populations of Asian and African descent have not been implemented.

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 also in differentially methylated regions. 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 interest is growing in specific cell types [132,133] and cell-type deconvolution algorithms to discern cell-type specific DNAm signals using whole-blood data [134]. Moreover, histone modifications have been implicated in asthma susceptibility and severity, response to ICS, 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 their findings must be validated to exclude spurious results due to differences in sample processing [136,137]. Despite this concern, many miRNAs have been consistently implicated in chronic respiratory and allergic diseases, highlighting their potential as possible therapeutic targets (eg, miR-206 and miRNA-21) [101-103]. Other plausible candidates in AEs are miRNAs involved in airway inflammation and 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 during the period reviewed 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 between host gene expression levels and microbial networks in the upper airways promotes AEs, the causative direction of those relationships remains unclear. Still, the authors proposed several 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 interferon γ [115].

Despite recent progress in genomic studies of AEs, the role of and interaction between different -omics layers in the modulation of the risk of AEs remain largely unexplored. In many cases, novel findings have yet to be validated in independent populations, and their prognostic potential is unclear. Key future determinants for identification of accurate biomarkers of AEs for precision medicine will include multiethnic 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.

References

1. Herrera-Luis E, Hernandez-Pacheco N, Vijverberg SJ, Flores C, Pino-Yanes M. Role of genomics in asthma exacerbations. Curr Opin Pulm Med. 2019;25(1):101-12.
2. Martin MJ, Beasley R, Harrison TW. Towards a personalised treatment approach for asthma attacks. Thorax. 2020;75(12):1119-29.
3. Asthma and Lung UK. Asthma data visualisations. Available at https://www.asthma.org.uk/support-us/campaigns/data-visualisations/
4. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med. 2016;14(1):113.
5. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008-2013. Ann Am Thorac Soc. 2018;15(3):348-56.
6. Luskin AT, Chipps BE, Rasouliyan L, Miller DP, Haselkorn T, Dorenbaum A. Impact of asthma exacerbations and asthma triggers on asthma-related quality of life in patients with severe or difficult-to-treat asthma. J Allergy Clin Immunol Pract. 2(5):544-52.e1-2.
7. Chipps BE, Haselkorn T, Rosén K, Mink DR, Trzaskoma BL, Luskin AT. Asthma Exacerbations and Triggers in Children in

TENOR: Impact on Quality of Life. J Allergy Clin Immunol Pract. 6(1):169-76.e2.

8. Rastogi D, Madhok N, Kipperman S. Caregiver Asthma Knowledge, Aptitude, and Practice in High Healthcare Utilizing Children: Effect of an Educational Intervention. Pediatr Allergy Immunol Pulmonol. 2013;26(3):128-39.

9. Major S, Vézina K, Tse SM. Lung Function of Children Following an Intensive Care Unit Admission for Asthma. Pediatr Allergy Immunol Pulmonol. 2021;34(1):1-6.

10. Briggs A, Nasser S, Hammerby E, Buchs S, Virchow JC. The impact of moderate and severe asthma exacerbations on quality of life: a post hoc analysis of randomised controlled trial data. J Patient Rep Outcomes. 2021;5(1):6.

11. O'Brian AL, Lemanske RF, Evans MD, Gangnon RE, Gern JE, Jackson DJ. Recurrent severe exacerbations in early life and reduced lung function at school age. J Allergy Clin Immunol. 2012;129(4):1162-4.

12. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, START Investigators Group. Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med. 2009;179(1):19-24.

13. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J. 2007;30(3):452-6.

14. Gold DR, Sordillo JE, Coull BA. Lung Function Tracking throughout Childhood: Growth Trajectories May Not Be Set in Stone. J Allergy Clin Immunol Pract. 2020;8(4):1272-4.

15. Hallas HW, Chawes BL, Arianto L, Rasmussen MA, Kunøe A, Stokholm J, et al. Children with Asthma Have Fixed Airway Obstruction through Childhood Unaffected by Exacerbations. J Allergy Clin Immunol Pract. 2020;8(4):1263-71.e3.

16. Winkler T, Frey U. Airway remodeling: Shifting the trigger point for exacerbations in asthma. J Allergy Clin Immunol. 2021;148(3):710-2.

17. Krings JG, Goss CW, Lew D, Samant M, McGregor MC, Boomer J, et al. Quantitative CT metrics are associated with longitudinal lung function decline and future asthma exacerbations: Results from SARP-3. J Allergy Clin Immunol. 2021;148(3):752-62.

18. Navanandan N, Hatoun J, Celedón JC, Liu AH. Predicting Severe Asthma Exacerbations in Children: Blueprint for Today and Tomorrow. J Allergy Clin Immunol Pract. 2021;9(7):2619-26.

19. Bloom CI, Palmer T, Feary J, Quint JK, Cullinan P. Exacerbation Patterns in Adults with Asthma in England. A Population-based Study. Am J Respir Crit Care Med. 2019;199(4):446-53.

20. Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. J Allergy Clin Immunol. 2012;130(2):332-42.e10.

21. Ramsahai JM, Hansbro PM, Wark PAB. Mechanisms and Management of Asthma Exacerbations. Am J Respir Crit Care Med. 2019;199(4):423-32.

22. Ioachimescu OC, Desai NS. Nonallergic Triggers and Comorbidities in Asthma Exacerbations and Disease Severity. Clin Chest Med. 2019;40(1):71-85.

23. di Palmo E, Cantarelli E, Catelli A, Ricci G, Gallucci M, Miniaci A, et al. The Predictive Role of Biomarkers and Genetics in Childhood Asthma Exacerbations. Int J Mol Sci. 2021;22(9):4651.

24. Lee DS, Gross E, Hotz A, Rastogi D. Comparison of severity of asthma hospitalization between African American and Hispanic children in the Bronx. J Asthma. 2020;57(7):736-42.

25. Rosser FJ, Forno E, Cooper PJ, Celedón JC. Asthma in Hispanics. An 8-year update. Am J Respir Crit Care Med. 2014;189(11):1316-27.

26. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. J Allergy Clin Immunol. 2014;134(3):547-53.e5.

27. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief. 2012;(94):1-8.

28. Oraka E, Iqbal S, Flanders WD, Brinker K, Garbe P. Racial and ethnic disparities in current asthma and emergency department visits: findings from the National Health Interview Survey, 2001-2010. J Asthma. 2013;50(5):488-96.

29. Engelkes M, Baan EJ, de Ridder MAJ, Svensson E, Prieto-Alhambra D, Lapi F, et al. Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study. Pediatr Allergy Immunol. 2020;31(5):496-505.

30. Silber JH, Rosenbaum PR, Calhoun SR, Reiter JG, Hill AS, Guevara JP, et al. Racial Disparities in Medicaid Asthma Hospitalizations. Pediatrics. 2017;139(1):e20161221.

31. Rumpel JA, Ahmedani BK, Peterson EL, Wells KE, Yang M, Levin AM, et al. Genetic ancestry and its association with asthma exacerbations among African American subjects with asthma. J Allergy Clin Immunol. 2012;130(6):1302-6.

32. Grossman NL, Ortega VE, King TS, Bleecker ER, Ampleford EA, Bacharier LB, et al. Exacerbation-prone asthma in the context of race and ancestry in Asthma Clinical Research Network trials. J Allergy Clin Immunol. 2019;144(6):1524-33.

33. Flores C, Ma S-FF, Pino-Yanes M, Wade MS, Pérez-Méndez L, Kittles RA, et al. African ancestry is associated with asthma risk in African Americans. PLoS One. 2012;7(1):e26807.

34. Brehm JM, Acosta-Pérez E, Klei L, Roeder K, Barmada MM, Boutaoui N, et al. African ancestry and lung function in Puerto Rican children. J Allergy Clin Immunol. 2012;129(6):1484-90.e6.

35. Pino-Yanes M, Thakur N, Gignoux CR, Galanter JM, Roth LA, Eng C, et al. Genetic ancestry influences asthma susceptibility and lung function among Latinos. J Allergy Clin Immunol. 2015;135(1):228-35.

36. Mersha TB, Qin K, Beck AF, Ding L, Huang B, Kahn RS. Genetic ancestry differences in pediatric asthma readmission are mediated by socioenvironmental factors. J Allergy Clin Immunol. 2021;148(5):1210-8.e4.

37. Gautam Y, Johansson E, Mersha TB. Multi-Omics Profiling Approach to Asthma: An Evolving Paradigm. J Pers Med. 2022;12(1):66.

38. NCBI Resource Coordinators. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res. 2016;44(D1):D7-19.

39. Duncan LE, Ostacher M, Ballon J. How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. Neuropsychopharmacology. 2019;44(9):1518-23.

40. El-Husseini ZW, Gosens R, Dekker F, Koppelman GH. The genetics of asthma and the promise of genomics-guided drug target discovery. Lancet Respir Med. 2020;8(10):1045-56.

41. Hernandez-Pacheco N, Flores C, Oh SS, Burchard EG, Pino-Yanes M. What Ancestry Can Tell Us About the Genetic Origins of Inter-Ethnic Differences in Asthma Expression. Curr Allergy Asthma Rep. 2016;16(8):53.

42. Hernandez-Pacheco N, Pino-Yanes M, Flores C. Genomic Predictors of Asthma Phenotypes and Treatment Response. Front Pediatr. 2019;7:6.

43. Schoettler N, Rodríguez E, Weidinger S, Ober C. Advances in asthma and allergic disease genetics: Is bigger always better? J Allergy Clin Immunol. 2019;144(6):1495-506.

44. Shriner D. Overview of Admixture Mapping. Curr Protoc Hum Genet. 2013;Chapter 1:Unit 1.23.

45. Gallagher MD, Chen-Plotkin AS. The Post-GWAS Era: From Association to Function. Am J Hum Genet. 2018;102(5):717-30.

46. Ghoussaini M, Mountjoy E, Carmona M, Peat G, Schmidt EM, Hercules A, et al. Open Targets Genetics: systematic identification of trait-associated genes using large-scale genetics and functional genomics. Nucleic Acids Res. 2021;49(D1):D1311-20.

47. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics. 2019;35(22):4851-3.

48. GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science. 2020;369(6509):1318-30.

49. Min JL, Hemani G, Hannon E, Dekkers KF, Castillo-Fernandez J, Luijk R, et al. Genomic and phenotypic insights from an atlas of genetic effects on DNA methylation. Nat Genet. 2021;53(9):1311-21.

50. Tse SM, Krajinovic M, Chauhan BF, Zemek R, Gravel J, Chalut D, et al. Genetic determinants of acute asthma therapy response in children with moderate-to-severe asthma exacerbations. Pediatr Pulmonol. 2019;54(4):378-85.

51. Uh S-T, Park J-S, Koo S-M, Kim Y-K, Kim KU, Kim M-A, et al. Association of Genetic Variants of NLRP4 with Exacerbation of Asthma: The Effect of Smoking. DNA Cell Biol. 2019;38(1):76-84.

52. Cho SH, Jo A, Casale T, Jeong SJ, Hong S-J, Cho JK, et al. Soy isoflavones reduce asthma exacerbation in asthmatic patients with high PAI-1-producing genotypes. J Allergy Clin Immunol. 2019;144(1):109-17.e4.

53. Tsai C-H, Wu AC, Chiang B-L, Yang Y-H, Hung S-P, Su M-W, et al. CEACAM3 decreases asthma exacerbations and modulates respiratory syncytial virus latent infection in children. Thorax. 2020;75(9):725-34.

54. Leiter K, Franks K, Borland ML, Coleman L, Harris L, Le Souëf PN, et al. Vitamin D receptor polymorphisms are associated with severity of wheezing illnesses and asthma exacerbations in children. J Steroid Biochem Mol Biol. 2020;201:105692.

55. Karimi L, Vijverberg SJ, Engelkes M, Hernandez-Pacheco N, Farzan N, Soares P, et al. ADRB2 haplotypes and asthma exacerbations in children and young adults: An individual participant data meta-analysis. Clin Exp Allergy. 2021;51(9):1157-71.

56. Herrera-Luis E, Lorenzo-Diaz F, Samedy-Bates LA, Eng C, Villar J, Rodriguez-Santana JR, et al. A deoxyribonuclease 1-like 3 genetic variant associates with asthma exacerbations. J Allergy Clin Immunol. 2021;147(3):1095-7.e10.

57. Hernandez-Pacheco N, Gorenjak M, Jurgec S, Corrales A, Jorgensen A, Karimi L, et al. Combined analysis of transcriptomic and genetic data for the identification of loci involved in glucocorticosteroid response in asthma. Allergy. 2021;76(4):1238-43.

58. Maroteau C, Espuela-Ortiz A, Herrera-Luis E, Srinivasan S, Carr F, Tavendale R, et al. LTA4H rs2660845 association with montelukast response in early and late-onset asthma. PLoS One. 2021;16(9):e0257396.

59. Li X, Christenson SA, Modena B, Li H, Busse WW, Castro M, et al. Genetic analyses identify GSDMB associated with asthma severity, exacerbations, and antiviral pathways. J Allergy Clin Immunol. 2021;147(3):894-909.

60. Dijk FN, Vijverberg SJ, Hernandez-Pacheco N, Repnik K, Karimi L, Mitratza M, et al. IL1RL1 gene variations are associated with asthma exacerbations in children and adolescents using inhaled corticosteroids. Allergy. 2020;75(4):984-9.

61. Edris A, de Roos EW, McGeachie MJ, Verhamme KMC, Brusselle GG, Tantisira KG, et al. Pharmacogenetics of inhaled corticosteroids and exacerbation risk in adults with asthma. Clin Exp Allergy. 2022;52(1):33-45.

62. Kim M-H, Chang HS, Lee J-U, Shim J-S, Park J-S, Cho Y-J, et al. Association of genetic variants of oxidative stress responsive kinase 1 (OXSR1) with asthma exacerbations in non-smoking asthmatics. BMC Pulm Med. 2022;22(1):3.

63. Kan M, Diwadkar AR, Shuai H, Joo J, Wang AL, Ong M-S, et al. Multiomics analysis identifies BIRC3 as a novel glucocorticoid response-associated gene. J Allergy Clin Immunol. 2022;149(6):1981-91.

64. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010;363 (13):1211-21.

65. Bouzigon E, Corda E, Aschard H, Dizier M-H, Boland A, Bousquet J, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. N Engl J Med. 2008;359(19):1985-94.

66. Flory JH, Sleiman PM, Christie JD, Annaiah K, Bradfield J, Kim CE, et al. 17q12-21 variants interact with smoke exposure as a risk factor for pediatric asthma but are equally associated with early-onset versus late-onset asthma in North Americans of European ancestry. J Allergy Clin Immunol. 2009;124(3):605-7.

67. Hernandez-Pacheco N, Kere M, Melén E. Gene-environment interactions in childhood asthma revisited; expanding the interaction concept. Pediatr Allergy Immunol. 2022;33(5):e13780.

68. Sunde RB, Thorsen J, Pedersen C-ET, Stokholm J, Bønnelykke K, Chawes B, et al. Prenatal tobacco exposure and risk of asthma and allergy outcomes in childhood. Eur Respir J. 2022;59(2):2100453.

69. Poli G, Fabi C, Bellet MM, Costantini C, Nunziangeli L, Romani L, et al. Epigenetic Mechanisms of Inflammasome Regulation. Int J Mol Sci. 2020;21(16):5758.

70. Hernandez-Pacheco N, Gorenjak M, Jurgec S, Corrales A, Jorgensen A, Karimi L, et al. Combined analysis of transcriptomic and genetic data for the identification of loci involved in glucocorticosteroid response in asthma. Allergy. 2021;76(4):1238-43.

71. Yan Q, Forno E, Herrera-Luis E, Pino-Yanes M, Yang G, Oh S, et al. A genome-wide association study of asthma hospitalizations in adults. J Allergy Clin Immunol. 2021;147(3):933-40.

72. Yan Q, Forno E, Herrera-Luis E, Pino-Yanes M, Qi C, Rios R, et al. A genome-wide association study of severe asthma exacerbations in Latino children and adolescents. Eur Respir J. 2021;57(4):2002693.

73. Herrera-Luis E, Espuela-Ortiz A, Lorenzo-Diaz F, Keys KL, Mak ACY, Eng C, et al. Genome-wide association study reveals a novel locus for asthma with severe exacerbations in diverse populations. Pediatr Allergy Immunol. 2021;32(1):106-15.

74. Ahluwalia TS, Eliasen AU, Sevelsted A, Pedersen C-ET, Stokholm J, Chawes B, et al. FUT2-ABO epistasis increases the risk of early childhood asthma and Streptococcus pneumoniae respiratory illnesses. Nat Commun. 2020;11(1):6398.

75. Son J-H, Park J-S, Lee J-U, Kim MK, Min S-A, Park C-S, et al. A genome-wide association study on frequent exacerbation of asthma depending on smoking status. Respir Med. 2022;199:106877.

76. Herrera-Luis E, Ortega VE, Ampleford EJ, Sio YY, Granell R, de Roos E, et al. Multi-ancestry genome-wide association study of asthma exacerbations. Pediatr Allergy Immunol. 2022;33(6):e13802.

77. Hernandez-Pacheco N, Farzan N, Francis B, Karimi L, Repnik K, Vijverberg SJ, et al. Genome-wide association study of inhaled corticosteroid response in admixed children with asthma. Clin Exp Allergy. 2019;49(6):789-98.

78. Levin AM, Gui H, Hernandez-Pacheco N, Yang M, Xiao S, Yang JJ, et al. Integrative approach identifies corticosteroid response variant in diverse populations with asthma. J Allergy Clin Immunol. 2019;143(5):1791-802.

79. Slob EMA, Richards LB, Vijverberg SJH, Longo C, Koppelman GH, Pijnenburg MWH, et al. Genome-wide association studies of exacerbations in children using long-acting beta2-agonists. Pediatr Allergy Immunol. 2021;32(6):1197-207.

80. Hernandez-Pacheco N, Vijverberg SJ, Herrera-Luis E, Li J, Sio YY, Granell R, et al. Genome-wide association study of asthma exacerbations despite inhaled corticosteroid use. Eur Respir J. 2021;57(5):2003388.

81. Hernandez-Pacheco N, Gorenjak M, Li J, Repnik K, Vijverberg SJ, Berce V, et al. Identification of ROBO2 as a Potential Locus Associated with Inhaled Corticosteroid Response in Childhood Asthma. J Pers Med. 2021;11(8):733.

82. Wang AL, Lahousse L, Dahlin A, Edris A, McGeachie M, Lutz SM, et al. Novel genetic variants associated with inhaled corticosteroid treatment response in older adults with asthma. Thorax. 2022;thoraxjnl-2021-217674. Online ahead of print.

83. Dahlin A, Sordillo JE, McGeachie M, Kelly RS, Tantisira KG, Lutz SM, et al. Genome-wide interaction study reveals age-dependent determinants of responsiveness to inhaled corticosteroids in individuals with asthma. PLoS One. 2020;15(3):e0229241.

84. Forno E, Zhang R, Jiang Y, Kim S, Yan Q, Ren Z, et al. Transcriptome-wide and differential expression network analyses of childhood asthma in nasal epithelium. J Allergy Clin Immunol. 2020;146(3):671-5.

85. Repapi E, Sayers I, Wain L V., Burton PR, Johnson T, Obeidat M, et al. Genome-wide association study identifies five loci associated with lung function. Nat Genet. 2010;42(1):36-44.

86. Burk RD, Chen Z, Saller C, Tarvin K, Carvalho AL, Scapulatempo-Neto C, et al. Integrated genomic and molecular characterization of cervical cancer. Nature. 2017;543(7645):378-84.

87. Lutz SM, Cho MH, Young K, Hersh CP, Castaldi PJ, McDonald M-L, et al. A genome-wide association study identifies risk loci for spirometric measures among smokers of European and African ancestry. BMC Genet. 2015;16:138.

88. Soler Artigas M, Wain LV, Miller S, Kheirallah AK, Huffman JE, Ntalla I, et al. Sixteen new lung function signals identified through 1000 Genomes Project reference panel imputation. Nat Commun. 2015;6:8658.

89. Hardin M, Cho MH, McDonald M-LL, Wan E, Lomas DA, Coxson HO, et al. A genome-wide analysis of the response to inhaled β2-agonists in chronic obstructive pulmonary disease. Pharmacogenomics J. 2016;16(4):326-35.

90. Adcock IM, Tsaprouni L, Bhavsar P, Ito K. Epigenetic regulation of airway inflammation. Curr Opin Immunol. 2007;19(6):694-700.

91. Adcock IM, Ito K, Barnes PJ. Histone deacetylation: an important mechanism in inflammatory lung diseases. COPD. 2005;2(4):445-55.

92. Herrera-Luis E, Mak ACY, Perez-Garcia J, Martin-Gonzalez E, Eng C, Beckman KB, et al. Admixture mapping of severe asthma exacerbations in Hispanic/Latino children and youth. Thorax. 2023;78(3):233-41.

93. Ortega VE, Daya M, Szefler SJ, Bleecker ER, Chinchilli VM, Phipatanakul W, et al. Pharmacogenetic studies of long-acting beta agonist and inhaled corticosteroid responsiveness in randomised controlled trials of individuals of African descent with asthma. Lancet Child Adolesc Heal. 2021;5(12):862-72.

94. Lee EY, Mak ACY, Hu D, Sajuthi S, White MJ, Keys KL, et al. Whole-Genome Sequencing Identifies Novel Functional Loci Associated with Lung Function in Puerto Rican Youth. Am J Respir Crit Care Med. 2020;202(7):962-72.

95. Sheikhpour M, Maleki M, Ebrahimi Vargoorani M, Amiri V. A review of epigenetic changes in asthma: methylation and acetylation. Clin Epigenetics. 2021;13(1):65.

96. Alashkar Alhamwe B, Alhamdan F, Ruhl A, Potaczek DP, Renz H. The role of epigenetics in allergy and asthma development. Curr Opin Allergy Clin Immunol. 2020;20(1):48-55.

97. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet. 2012;13(7):484-92.

98. Curtin JA, Simpson A, Belgrave D, Semic-Jusafagic A, Custovic A, Martinez FD. Methylation of IL-2 promoter at birth alters the risk of asthma exacerbations during childhood. Clin Exp Allergy. 2013;43(3):304-11.

99. Wang AL, Gruzieva O, Qiu W, Kebede Merid S, Celedón JC, Raby BA, et al. DNA methylation is associated with inhaled corticosteroid response in persistent childhood asthmatics. Clin Exp Allergy. 2019;49(9):1225-34.

100. Bustamante J, Zhang S-Y, Boisson B, Ciancanelli M, Jouanguy E, Dupuis-Boisson S, et al. Immunodeficiencies at the Interface of Innate and Adaptive Immunity. In: Clinical Immunology. Elsevier; 2019. p. 509-22.e1.

101. Weidner J, Bartel S, Kılıç A, Zissler UM, Renz H, Schwarze J, et al. Spotlight on microRNAs in allergy and asthma. Allergy. 2021;76(6):1661-78.

102. Tubita V, Callejas-Díaz B, Roca-Ferrer J, Marin C, Liu Z, Wang DY, et al. Role of microRNAs in inflammatory upper airway diseases. Allergy. 2021;76(7):1967-80.

103. Cañas JA, Rodrigo-Muñoz JM, Sastre B, Gil-Martinez M, Redondo N, Del Pozo V. MicroRNAs as Potential Regulators of Immune Response Networks in Asthma and Chronic Obstructive Pulmonary Disease. Front Immunol. 2020;11:608666.

104. Midyat L, Gulen F, Karaca E, Ozkinay F, Tanac R, Demir E, et al. MicroRNA expression profiling in children with different asthma phenotypes. Pediatr Pulmonol. 2016;51(6):582-7.

105. Tian M, Zhou Y, Jia H, Zhu X, Cui Y. The Clinical Significance of Changes in the Expression Levels of MicroRNA-1 and Inflammatory Factors in the Peripheral Blood of Children with Acute-Stage Asthma. Biomed Res Int. 2018;2018:7632487.

106. Korde A, Ahangari F, Haslip M, Zhang X, Liu Q, Cohn L, et al. An endothelial microRNA-1-regulated network controls eosinophil trafficking in asthma and chronic rhinosinusitis. J Allergy Clin Immunol. 2020;145(2):550-62.

107. Kho AT, McGeachie MJ, Moore KG, Sylvia JM, Weiss ST, Tantisira KG. Circulating microRNAs and prediction of asthma exacerbation in childhood asthma. Respir Res. 2018;19(1):128.

108. Wardzyńska A, Pawełczyk M, Rywaniak J, Kurowski M, Makowska JS, Kowalski ML. Circulating MicroRNAs and T-Cell Cytokine Expression Are Associated With the Characteristics of Asthma Exacerbation. Allergy Asthma Immunol Res. 2020;12(1):125-36.

109. Gomez JL, Chen A, Diaz MP, Zirn N, Gupta A, Britto C, et al. A Network of Sputum MicroRNAs Is Associated with Neutrophilic Airway Inflammation in Asthma. Am J Respir Crit Care Med. 2020;202(1):51-64.

110. Tiwari A, Hobbs BD, Li J, Kho AT, Amr S, Celedón JC, et al. Blood miRNAs Are Linked to Frequent Asthma Exacerbations in Childhood Asthma and Adult COPD. Noncoding RNA. 2022;8(2):27.

111. Mattes J, Collison A, Plank M, Phipps S, Foster PS. Antagonism of microRNA-126 suppresses the effector function of TH2 cells and the development of allergic airways disease. Proc Natl Acad Sci U S A. 2009;106(44):18704-9.

112. Kho AT, Sharma S, Davis JS, Spina J, Howard D, McEnroy K, et al. Circulating MicroRNAs: Association with Lung Function in Asthma. PLoS One. 2016;11(6):e0157998.

113. Li H, Wang H, Sokulsky L, Liu S, Yang R, Liu X, et al. Single-cell transcriptomic analysis reveals key immune cell phenotypes in the lungs of patients with asthma exacerbation. J Allergy Clin Immunol. 2021;147(3):941-54.

114. McCauley KE, Flynn K, Calatroni A, DiMassa V, LaMere B, Fadrosh DW, et al. Seasonal airway microbiome and transcriptome interactions promote childhood asthma exacerbations. J Allergy Clin Immunol. 2022;150(1):204-13.

115. Klaile E, Klassert TE, Scheffrahn I, Müller MM, Heinrich A, Heyl KA, et al. Carcinoembryonic antigen (CEA)-related cell adhesion molecules are co-expressed in the human lung and their expression can be modulated in bronchial epithelial cells by non-typable Haemophilus influenzae, Moraxella catarrhalis, TLR3, and type I and II interferons. Respir Res. 2013;14:85.

116. Hoda U, Pavlidis S, Bansal AT, Takahashi K, Hu S, Ng Kee Kwong F, et al. Clinical and transcriptomic features of persistent exacerbation-prone severe asthma in U-BIOPRED cohort. Clin Transl Med. 2022;12(4):e816.

117. Cho MH, Hobbs BD, Silverman EK. Genetics of chronic obstructive pulmonary disease: understanding the pathobiology and heterogeneity of a complex disorder. Lancet Respir Med. 2022;10(5):485-96.

118. DeMeo DL. Sex and Gender Omic Biomarkers in Men and Women With COPD: Considerations for Precision Medicine. Chest. 2021;160(1):104-13.

119. Regan EA, Hersh CP, Castaldi PJ, DeMeo DL, Silverman EK, Crapo JD, et al. Omics and the Search for Blood Biomarkers in Chronic Obstructive Pulmonary Disease. Insights from COPDGene. Am J Respir Cell Mol Biol. 2019;61(2):143-9.

120. Bønnelykke K, Sleiman P, Nielsen K, Kreiner-Møller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet. 2014;46(1):51-5.

121. Atkinson EG, Maihofer AX, Kanai M, Martin AR, Karczewski KJ, Santoro ML, et al. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. Nat Genet. 2021;53(2):195-204.

122. Dahlin A, Denny J, Roden DM, Brilliant MH, Ingram C, Kitchner TE, et al. CMTR1 is associated with increased asthma exacerbations in patients taking inhaled corticosteroids. Immun Inflamm Dis. 2015;3(4):350-9.

123. Sordillo JE, Lutz SM, Jorgenson E, Iribarren C, McGeachie M, Dahlin A, et al. A polygenic risk score for asthma in a large racially diverse population. Clin Exp Allergy. 2021;51(11):1410-20.

124. Namjou B, Lape M, Malolepsza E, DeVore SB, Weirauch MT, Dikilitas O, et al. Multiancestral polygenic risk score for pediatric asthma. J Allergy Clin Immunol. 2022;S0091-6749(22)00660-1.

125. Kothalawala DM, Kadalayil L, Curtin JA, Murray CS, Simpson A, Custovic A, et al. Integration of Genomic Risk Scores to Improve the Prediction of Childhood Asthma Diagnosis. J Pers Med. 2022;12(1):75.

126. Dijk FN, Folkersma C, Gruzieva O, Kumar A, Wijga AH, Gehring U, et al. Genetic risk scores do not improve asthma prediction in childhood. J Allergy Clin Immunol. 2019;144(3):857-60.e7.

127. Wu C, Zhu J, King A, Tong X, Lu Q, Park JY, et al. Novel strategy for disease risk prediction incorporating predicted gene expression and DNA methylation data: a multi-phased study of prostate cancer. Cancer Commun (Lond). 2021;41(12):1387-97.

128. Hu X, Qiao D, Kim W, Moll M, Balte PP, Lange LA, et al. Polygenic transcriptome risk scores for COPD and lung function improve cross-ethnic portability of prediction in the NHLBI TOPMed program. Am J Hum Genet. 2022;109(5):857-70.

129. Kilanowski A, Chen J, Everson T, Thiering E, Wilson R, Gladish N, et al. Methylation risk scores for childhood aeroallergen sensitization: Results from the LISA birth cohort. Allergy. 2022;77(9):2803-17.

130. Montesinos López OA, Montesinos López A, Crossa J. Overfitting, Model Tuning, and Evaluation of Prediction Performance. In: Montesinos López OA, Montesinos López A, Crossa J, editors. Multivariate Statistical Machine Learning Methods for Genomic Prediction. 1st ed. Springer Cham; 2022. p. 109-139.

131. Lee TY, Petkau J, Sadatsafavi M. Long-Term Natural History of Severe Asthma Exacerbations and Their Impact on the Disease Course. Ann Am Thorac Soc. 2022;19(6):907-15.

132. Bélanger É, Laprise C. Could the Epigenetics of Eosinophils in Asthma and Allergy Solve Parts of the Puzzle? Int J Mol Sci. 2021;22(16):8921.

133. Hudon Thibeault A-A, Laprise C. Cell-Specific DNA Methylation Signatures in Asthma. Genes (Basel). 2019;10(11):932.

134. Rahmani E, Schweiger R, Rhead B, Criswell LA, Barcellos LF, Eskin E, et al. Cell-type-specific resolution epigenetics without the need for cell sorting or single-cell biology. Nat Commun. 2019;10(1):3417.

135. Helling BA, Sobreira DR, Hansen GT, Sakabe NJ, Luo K, Billstrand C, et al. Altered transcriptional and chromatin responses to rhinovirus in bronchial epithelial cells from adults with asthma. Commun Biol. 2020;3(1):678.

136. Kim SH, MacIntyre DA, Sykes L, Arianoglou M, Bennett PR, Terzidou V. Whole Blood Holding Time Prior to Plasma Processing Alters microRNA Expression Profile. Front Genet. 2021;12:818334.

137. Chorley BN, Atabakhsh E, Doran G, Gautier J-C, Ellinger-Ziegelbauer H, Jackson D, et al. Methodological considerations for measuring biofluid-based microRNA biomarkers. Crit Rev Toxicol. 2021;51(3):264-82.

138. Taka S, Tzani-Tzanopoulou P, Wanstall H, Papadopoulos NG. MicroRNAs in Asthma and Respiratory Infections: Identifying Common Pathways. Allergy Asthma Immunol Res. 2020;12(1):4-23.

▌ **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