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Multi-ancestry genome-wide association study of asthma exacerbations

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Abbreviations: 1KGP, 1000 Genomes Project; CDK6, cyclin-dependent kinase 6; CI, confidence interval; GAG, glycosaminoglycan; GTEx, genotype-tissue expression; GWAS, genome-wide association study; LPS, lipopolysaccharide; MAF, minor allele frequency; meQTL, methylation quantitative trait loci; OR, odds ratio; PPAR-α, peroxisome proliferator-activating receptor α; RR, relative risk; SNP, single-nucleotide polymorphism; TLR4, Toll-like receptor 4; TNFα, tumor necrosis factor α.

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Abstract

Background: Asthma exacerbations are a serious public health concern due to high healthcare resource utilization, work/school productivity loss, impact on quality of life, and risk of mortality. The genetic basis of asthma exacerbations has been studied in several populations, but no prior study has performed a multi-ancestry meta-analysis of genome-wide association studies (meta-GWAS) for this trait. We aimed to identify common genetic loci associated with asthma exacerbations across diverse populations and to assess their functional role in regulating DNA methylation and gene expression.

Methods: A meta-GWAS of asthma exacerbations in 4989 Europeans, 2181 Hispanics/Latinos, 1250 Singaporean Chinese, and 972 African Americans analyzed 9.6 million genetic variants. Suggestively associated variants ($p \leq 5 \times 10^{-5}$) were assessed for replication in 36,477 European and 1078 non-European asthma patients. Functional effects on DNA methylation were assessed in 595 Hispanic/Latino and African American asthma patients and in publicly available databases. The effect on gene expression was evaluated in silico.

Results: One hundred and twenty-six independent variants were suggestively associated with asthma exacerbations in the discovery phase. Two variants independently replicated: rs12091010 located at vascular cell adhesion molecule-1/exostosin like glycosyltransferase-2 (*VCAM1/EXTL2*) (discovery: odds ratio ($OR_{T\ allele}$) = 0.82, $p = 9.05 \times 10^{-6}$ and replication: $OR_{T\ allele} = 0.89$, $p = 5.35 \times 10^{-3}$) and rs943126 from pantothenate kinase 1 (*PANK1*) (discovery: $OR_{C\ allele} = 0.85$, $p = 3.10 \times 10^{-5}$ and replication: $OR_{C\ allele} = 0.89$, $p = 1.30 \times 10^{-2}$). Both variants regulate gene expression of genes where they locate and DNA methylation levels of nearby genes in whole blood.

Conclusions: This multi-ancestry study revealed novel suggestive regulatory loci for asthma exacerbations located in genomic regions participating in inflammation and host defense.

KEYWORDS
asthma exacerbations, *EXTL2*, GWAS, *PANK1*, single-nucleotide polymorphism

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1 | INTRODUCTION

Asthma is a common chronic inflammatory airway disorder affecting over 300 million people worldwide. The disparities in asthma prevalence across populations reflect a complex interplay between environmental exposures (i.e., air pollution and viral infections), behavioral and socioeconomic factors (i.e., treatment adherence and healthcare access), and genetic ancestry, which is inferred from whole-genome variation and tracks geographic and historical factors and the aforementioned factors influencing asthma prevalence.[1,2]

Asthma exacerbations are defined as worsening of respiratory symptoms requiring hospitalization, unscheduled/emergency asthma care, and/or use of systemic corticosteroids.[3] Prevention of asthma exacerbations is a major public health priority due to their associated consequences on health (i.e., decreased quality of life, accelerated decline in lung function, or mortality), school attendance, work productivity, and healthcare costs.[1,4,5] To date, the best predictor of future exacerbations is the occurrence of one in the previous year.[6] Thus, identifying potential biomarkers to guide the reduction and prevention of exacerbations is a priority for therapeutics development and for precision medicine of asthma.

With the advent of high-throughput sequencing and genotyping technologies, the study of the genetic contributions to asthma exacerbations has shifted from hypothesis-driven, limited candidate-gene strategies to genome-wide association studies (GWAS).[7–14] Pharmacogenomics studies of asthma exacerbations as an outcome of treatment response have identified five suggestive associations for asthma exacerbations despite inhaled corticosteroids (*CMTR1*,[9] *APOBEC3B-APOBEC3C*,[8] and *CACNA2D3-WNT5A*[11]), or long-acting beta2-agonists (*TBX3* and *EPHA7*).[10] Beyond pharmacogenomics, other studies have focused on asthma exacerbations independently of treatment. In European-descent populations, *CDHR3*, *CTNNA3*, and *HLA-DQB1* have been associated with severe asthma exacerbations.[7,13] More recently, the representation of ethnically diverse populations has increased in GWAS of asthma exacerbations. A meta-analysis of GWAS in Hispanic/Latino children identified a single-nucleotide polymorphism (SNP) at *FLJ22447* that modulated *KCNJ2-AS1* expression in nasal epithelium through DNA methylation.[12] In Hispanic/Latinos and African Americans, a genome-wide significant locus for asthma with exacerbations regulated *LINC01913* lung gene expression and DNA methylation levels of the *PKDCC* gene in whole blood.[14] However, none of those studies has approached the search for genetic determinants of asthma exacerbations independently of treatment from a multi-ancestry framework.

To improve our understanding on genetic and biological mechanisms of asthma exacerbations across multiple populations, we conducted the first multi-ancestry meta-analysis of GWAS of asthma exacerbations independently of treatment and attempted to validate previous associations. Then, we conducted *in silico* and *in vivo* downstream analyses to assess the potential functional effects of the associated SNPs over DNA methylation and gene expression.

Key Message

A large multi-ancestry meta-analysis of GWAS of asthma exacerbations revealed two novel susceptibility loci located close to *PANK1* and at the intergenic region of *VCAM1* and *EXTL2*. These loci decreased *PANK1* and *EXTL2* gene expression in whole blood, respectively. Both genetic variants were associated with DNA methylation levels at CpG sites nearby. Our results identified two gene targets for asthma exacerbations that should be further explored to assess their specific role in asthma.

2 | METHODS

2.1 | Study design and study populations

We performed a two-stage study to identify genetic variants associated with asthma exacerbations, defined as a binary variable based on the presence of emergency care, hospitalizations, or administration of systemic corticosteroids because of asthma. We also considered a definition of moderate exacerbations,[3] comprising unscheduled general practitioner or pulmonary specialist visits and school absence, as no information on the former variables was available for some studies. A period of 6–24 months or ever was considered depending on the data available for each study (Tables S1 and S2). In the discovery phase, we performed a multi-ancestry meta-analysis of GWAS of asthma exacerbations in 9392 patients with asthma from 12 studies, including 4989 European-descents from nine studies, 2181 Hispanics/Latinos, 1250 Singaporean Chinese, and 972 African Americans. We attempted to replicate the findings from the discovery phase in a total of 37,555 participants with asthma, including 36,477 Europeans from seven studies, 877 Latinos from two studies, and 201 Filipinos from one study (Table S2). A detailed description of each study is available in the Appendix S1. All studies included were approved by their respective Institutional review boards, and written informed consent was provided by participants or their parents/caregivers. All methods followed the Declaration of Helsinki guidelines.

Assessment of genetic ancestry was performed using principal component analysis. The Haplotype Reference Consortium (r1.1 2016)[15] was used as the reference imputation panel for most studies, except for Avon Longitudinal Study of Parents and Children (ALSPAC) and Singapore Cross Sectional Genetic Epidemiology Study (SCSGES), which used the phase 3 of the 1000 Genomes Project (1KGP).[16] Genotyping and imputation procedures for the discovery and replication studies are detailed in the Appendix S1 and Tables S1 and S2.

2.2 | Association analysis

Association between genetic variants and asthma exacerbations was tested using logistic regression models including age, sex, and principal components from the genotype matrix (if needed to correct for population stratification) (Table S1). Analyses were conducted separately for each study using PLINK 2.0,[17] EPACTS 3.2.6[18] or rvtests 2.1.0.[19] Results were filtered with the EasyQC software[20] to retain variants with a minor allele frequency (MAF) ≥ 1% and imputation quality $R^2 \geq .3$, absolute value of the beta coefficient <10, standard error of the beta included in the interval [0,10], and minor allele cut-off ≥6.

In the discovery phase, genetic variants that were available in at least two ethnic-specific studies were meta-analyzed with METASOFT,[21] using fixed-effects or random-effects models based on the heterogeneity among studies (measured by the Cochran's *Q* test *p*-value). Ethnic-specific results were then combined in a multi-ancestry meta-analysis. Independent variants ($r^2 \leq .8$) with suggestive association[22] at $p \leq 5 \times 10^{-5}$ within 1 Megabase were identified with GCTA-COJO v1.93.2[23] using the 1KGP reference.[16] These variants were evaluated in the replication stage, following the same procedures as in the discovery phase. Evidence of replication was considered if the variants showed consistent direction of effects with the discovery stage at $p \leq .05$.

2.3 | Assessment of shared genetic basis of asthma exacerbations with other traits

To identify groups of genes previously associated with other traits, we used a Gene-Set Enrichment Analysis (GSEA), as implemented in FUMA GWAS[24] via the *GENE2FUNC* algorithm, and queried the GWAS catalog.[25] SNPs with $p \leq 1 \times 10^{-4}$ in the discovery phase of the meta-analysis of GWAS were mapped to the closest gene using the UCSC Table Browser tool.[26] A false discovery rate (FDR) of 5% was used to declare significance.

To estimate the pairwise genome-wide genetic correlations (R_g) between asthma exacerbations and other traits, we compared our findings with publicly available GWAS summary statistics via LD score regression using LDHub.[27] As most of the GWAS have been conducted in European populations, the analysis was restricted to predominantly European-descent individuals to maximize the statistical power. A Bonferroni-corrected significance threshold of $p < .05/711$ traits $= 6.48 \times 10^{-5}$ was applied.

2.4 | Sensitivity analysis

To assess the robustness of the genetic associations, we conducted sensitivity analyses for the time-dependent probability occurrence of exacerbations, the effect of Body Mass Index (BMI), obesity, asthma severity, and age group. Moreover, we evaluated the association of the variants with asthma susceptibility, as detailed in the Appendix S1. Studies from the discovery stage that had covariate data available were considered.

2.5 | Methylation profiling and quality control

Whole blood DNA methylation from Hispanics/Latinos and African Americans was profiled using the Infinium HumanMethylation450 BeadChip or the Infinium Methylation EPIC BeadChip arrays. Briefly, low-quality probes and samples, outliers of DNA methylation, and samples with sex mismatch or mixed genotype distributions on the control SNP probes were excluded. Standard background correction, dye-bias correction, inter-array normalization, and probe-type bias adjustment were performed, and beta values were transformed to *M*-values for better statistical performance. Quality control is detailed in the Appendix S1.

2.6 | Functional assessment of associated SNPs

DNA methylation quantitative trait loci (meQTL) analyses were conducted using fastQTL[28] for CpG sites within 1 Mb of SNPs with MAF ≥ 0.01 in at least 10 samples, separately in 139 Mexican Americans and 241 Puerto Ricans from Genes-Environments & Admixture in Latino Americans (GALA II) and 215 African Americans from the Study of African Americans, Asthma, Genes & Environments (SAGE) studies. Linear regression models were corrected for asthma exacerbations status, age, sex, genetic ancestry, ReFACTor components as a proxy of cell heterogeneity, and methylation batch (when appropriate). The results from Mexican Americans and Puerto Ricans assayed with different methylation arrays were then meta-analyzed for each sub-ethnic group with METASOFT.[21] SNP-CpG pairs were considered significant at Storey *q*-value <.05. In silico evidence of functional effects of variants on gene expression and DNA methylation was assessed using QTLbase,[29] Genotype-Tissue Expression (GTEx) v8 Portal,[30] PhenoScanner v2[31] and eFORGE-TF.[32] Long-distance chromatin interactions were determined using the ChiCP tool.[33]

2.7 | Validation of previous associations

A literature search for all studies reporting genetic loci significantly associated with asthma exacerbations was conducted, as described in the Appendix S1. Association results in the discovery stage were extracted and significance threshold was defined as $p = .05/$ number of tested SNPs to adjust for multiple testing.

3 | RESULTS

3.1 | Characteristics of the patients

In the discovery phase, we analyzed 2781 exacerbators and 6611 non-exacerbators; 53.1% were predominantly Europeans, 23.2% Hispanics/Latinos, 13.3% Singaporean Chinese, and 10.3% African Americans. The percentage of exacerbators ranged from 9.1% to 65.2% in Europeans, and reached 58.8% in Hispanics/Latinos, 46.1% in African Americans, and 3.4% in Singaporeans. The replication phase included 37,555 individuals with asthma (3030 exacerbators and 34,525 non-exacerbators) where most participants were of European descent (97.1%), followed by Latinos (2.3%) and Filipinos (0.5%). The percentage of exacerbators ranged from 4.8% to 65.2% in Europeans, reached approximately 43% in Latinos, and 1.3% in Filipinos (Tables S1 and S2). Regarding sex, 51.7% and 42.9% were male participants in the discovery and replication phases, respectively.

3.2 | Discovery phase

The quantile–quantile plots did not show major genomic inflation due to population stratification in each individual study (Figure S1), the combined results from individuals of European-descent (Figure S2), or the multi-ancestry meta-analysis (Figure S3). In the multi-ancestry meta-analysis of 9,634,748 variants, 447 SNPs exhibited suggestive association (Table S3). The most significant association was the intronic SNP rs6888198 within the cadherin-12 (*CDH12*) gene at chromosome 5p14.3 (odds ratio [OR] for C allele: 1.37, 95% confidence interval [CI]: 1.23–1.54, $p = 1.95 \times 10^{-8}$) (Figure 1, Figure S4).

3.3 | Replication phase

Fifteen of the 126 independent variants identified in the discovery phase were not available for replication as they were mostly present in African Americans and Hispanics/Latinos (Table S3). Two of the 106 variants present in more than one ethnic group were consistently associated with asthma exacerbations (Table 1): rs12091010 [*VCAM1/EXTL2*, OR for T allele: 0.89 (0.82–0.97), $p = 5.35 \times 10^{-3}$] (Figure 2) and rs943126 [*PANK1*, OR for C allele: 0.92 (0.86–0.98), $p = 1.30 \times 10^{-2}$] (Figure 3). In the meta-analysis across both phases, these variants reached an association *p*-value of 4.23×10^{-7} and 4.93×10^{-6}, respectively. From five variants that were present only in non-Europeans in the replication stage, none exhibited $p < .05$ in any other population group (Table S4). Even though rs6888198 reached genome-wide significance in the discovery and showed consistent effects among Europeans in the replication phase, this SNP had opposite effects in Latinos and Filipinos, which resulted in the lack of replication in the multi-ancestry replication phase (Table 1, Figure S5).

3.4 | Gene-set enrichment and genome-wide genetic correlation analysis

Enrichment analysis of associations from the multi-ancestry discovery GWAS including 959 SNPs associated with asthma exacerbations at $p \le 1 \times 10^{-4}$ revealed significant enrichment in several traits, including treatment response (min $p = 2.77 \times 10^{-6}$), neurological conditions (min $p = 4.62 \times 10^{-5}$), obesity (min $p = 6.52 \times 10^{-5}$), or waist-to-hip ratio (min $p = 1.88 \times 10^{-7}$) (Table S5).

A total of 16 traits exhibited genetic correlation with asthma exacerbations at $p < .05$ (Table S6), including wheeze or whistling in the last year ($R_g = 0.47$, $p = 1.01 \times 10^{-2}$), emphysema/chronic bronchitis ($R_g = 0.55$, $p = 3.89 \times 10^{-2}$), asthma ($R_g = 0.32$, $p = 3.99 \times 10^{-2}$), and BMI ($R_g = 0.19$, $p = 4.76 \times 10^{-2}$). However, the associations did not remain significant after Bonferroni correction.

3.5 | Sensitivity analysis

To assess the robustness of associations that replicated across stages to the time-dependent probability of occurrence of exacerbations, stratified analyses were performed in European-descents from the discovery stage that reported exacerbations for 6 vs. 12 months. Consistent effects per period were observed across periods (Table 2).

As the post-GWAS analyses revealed significant enrichment/correlation at $p < .05$ with fat mass/distribution, the association of rs12091010 and rs943126 after additional adjustment by BMI/obesity was examined in individuals from the discovery phase with BMI data available. Moreover, the effect of asthma severity alone or combined with BMI/obesity on the genetic association exacerbations was evaluated. The effects sizes of the genetic association after additional adjustment by these variables remained consistent with the effects reported in the discovery stage (Table S7).

We next investigated if the observed effects could differ across age groups in those studies that analyzed exclusively children or adults, but the effect sizes remained consistent across age groups (Table S8). Moreover, we assessed if the effects could be driven by the underlying asthma syndrome, rather than asthma exacerbations, and no significant association with asthma was found in results from the UK Biobank or the Michigan Genomics Initiative (Table S9).

3.6 | Functional exploration of variants associated with asthma exacerbations

We next assessed the association between DNA methylation levels in whole blood at 525 and 538 CpG sites with rs12091010 and rs943126, respectively. A total of 7 and 1 SNP-CpG pairs for rs943126 and rs12091010 exhibited Storey $q < .05$, respectively (Table 3 and Table S10). Two of these replicated consistently in

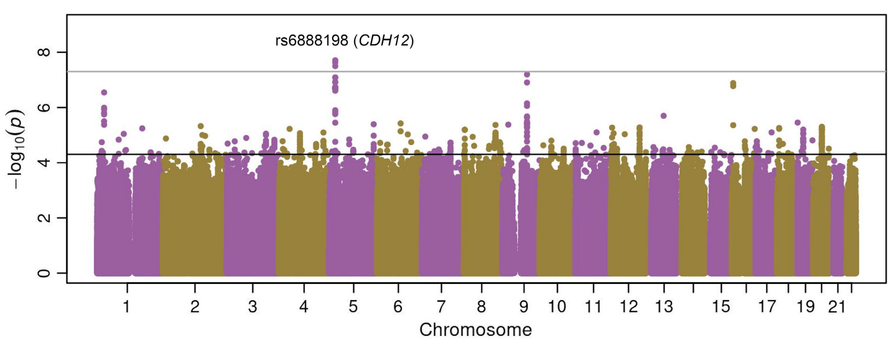

FIGURE 1 Manhattan plot of the results of the discovery stage of the multi-ancestry meta-analysis of GWAS of asthma exacerbations (represented as -$\log_{10}$ *p*-value on the *y*-axis) along the chromosome position of the variants analyzed (*x*-axis). The suggestive ($p = 5 \times 10^{-5}$) and genome-wide ($p = 5 \times 10^{-8}$) significance thresholds are indicated by the black line and dark gray lines

TABLE 1 Association results for the top hit in the discovery stage and sentinel variants with significant and consistent effects in the discovery and replication phases, and the meta-analysis across both phases

			Discovery			Replication			Meta-analysis (discovery and replication)		
ID[a]	rsID	Closest gene	OR (95% CI)	*p*	Cochran's Q *p*	OR (95% CI)	*p*	Cochran's Q *p*	OR (95% CI)	*p*	Cochran's Q *p*
1:101210560:C:T	rs12091010	*EXTL2*	0.82 (0.75–0.90)	9.05E-06	4.83E-01	0.89 (0.82–0.97)	5.35E-03	4.92E-01	0.86 (0.81–0.91)	4.23E-07	4.47E-01
5:22659406:T:C	rs6888198	*CDH12*	1.37 (1.23–1.54)	1.95E-08	5.82E-01	1.02 (0.90–1.15)	7.72E-01	7.18E-01	1.24 (1.05–1.45)	2.41E-06	1.89E-02
10:91376299:T:C	rs943126	*PANK1*	0.85 (0.78–0.92)	3.10E-05	8.01E-02	0.92 (0.86–0.98)	1.30E-02	3.87E-01	0.89 (0.85–0.94)	4.93E-06	7.91E-02

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; *p*, *p*-value.
[a]The variant identifier corresponds to chromosomal position (hg19) followed by non-tested allele and tested allele.

Europeans for rs943126 (cg25770176 and cg00475140). *In silico* analyses revealed 10 SNP-CpGs pairs, 3 of which showed consistent effects in Hispanics/Latinos and African Americans at Storey $q < .05$ (Tables S11 and S12) including the previous two pairs and rs943126-cg03948048. The eight significant CpG sites in minority children showed significant enrichment ($q < .001$) in transcription factor (TF) motifs in lung (Table S13). Besides, the T allele of rs12091010 was associated with decreased *EXTL2* expression in whole blood from Europeans, according to PhenoScanner.[31] The C allele of rs943126 was associated with increased expression of *PANK1* in whole blood from Europeans (Table S14). Both variants showed evidence of long-range chromatin interaction with several genes in lymphoblastoid cells, including *VCAM1* and *EXTL2* for rs12091010 and *PANK1* for rs943126 (Table S15).

3.7 | Validation of previous associations

We next examined 47 previous genetic loci for asthma exacerbations[7,8,12,13,34–36] and moderate-to-severe asthma[37] for association with asthma exacerbations in the discovery phase. A total of 5 variants had $p < .05$ in Europeans, 2 in Hispanics/Latinos, 5 in African Americans, and 1 in Singaporean Chinese (Table S16). These were in loci previously associated with asthma exacerbations (*GSDMB*, *RAD50*, *HLA-DQB1*, *ADAM33*, *VDR*, and *CDHR3*) or moderate-to-severe asthma (*IKZF3*, *TSLP*, *MUC5AC*, *C11orf30*, *SMAD3*, and *WDR36*). However, none of the SNPs exceeded the stringent Bonferroni-corrected threshold for significance ($p = .05/47 = 1.06 \times 10^{-3}$).

4 | DISCUSSION

To our knowledge, this is the first multi-ancestry meta-analysis of GWAS of asthma exacerbations independently of treatment including European, Hispanic/Latino, Asian, and African American patients with asthma. In our combined analysis of 46,947 individuals with asthma, two regulatory SNPs were significantly and consistently associated with asthma exacerbations in most of the studies included in the discovery and replication phases, independently of the type of exacerbation and the time period for which the exacerbation status was assessed. The SNP rs120910109 was located in the intergenic region of the *VCAM1*/*EXTL2* genes, whereas rs943126 was harbored within intron 1 of *PANK1*.

VCAM1 encodes a surface protein predominantly expressed in endothelial cells that modulates leukocyte adhesion and trans-endothelial migration in response to pro-inflammatory cytokines, and lipopolysaccharide (LPS) among other factors.[38,39] VCAM1 is involved in cancer progression and several immunological disorders, including asthma.[38] In the ovalbumin mice model, anti-VCAM1 reduced airway hyperresponsiveness and eosinophilic inflammation.[40] On the other hand, *EXTL2* encodes an enzyme that controls glycosaminoglycan (GAG) biosynthesis via transference of N-acetylgalactosamine and

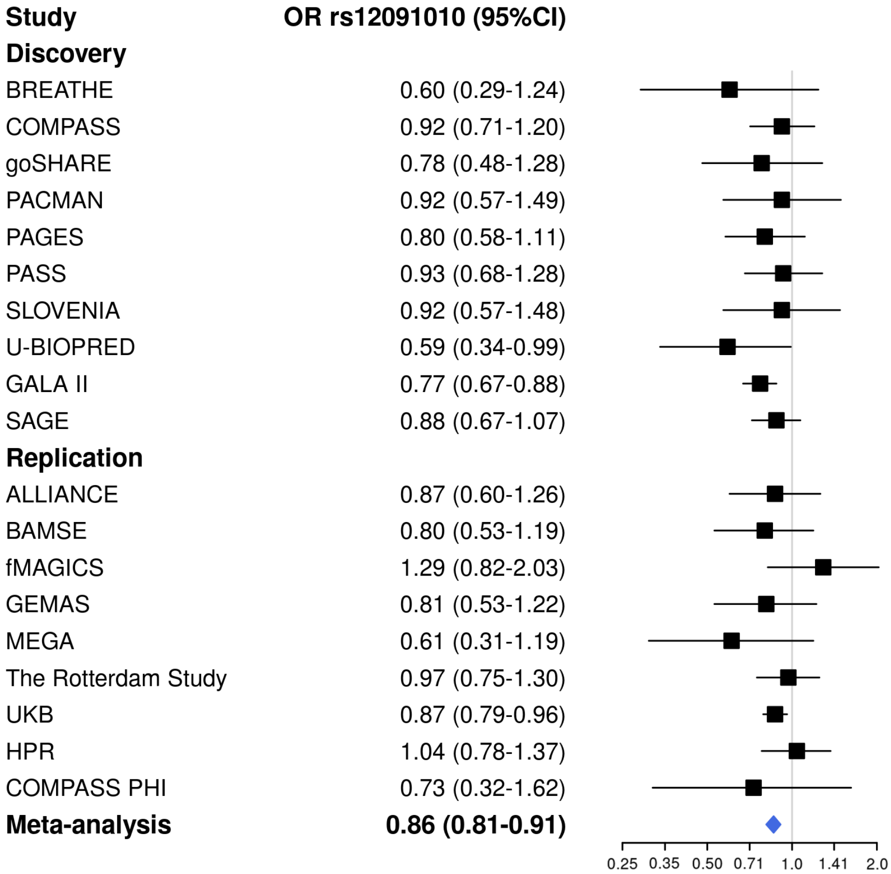

FIGURE 2 Forest plot of the association results for rs12091010 (*VCAM1/EXTL2*) in the meta-analysis of GWAS of asthma exacerbations. ALSPAC (discovery), SCSGES (discovery), and the subset of samples from BREATHE genotyped with the Illumina Infinium CoreExome-24 BeadChip (replication) had no genotyped or imputed data for rs12091010

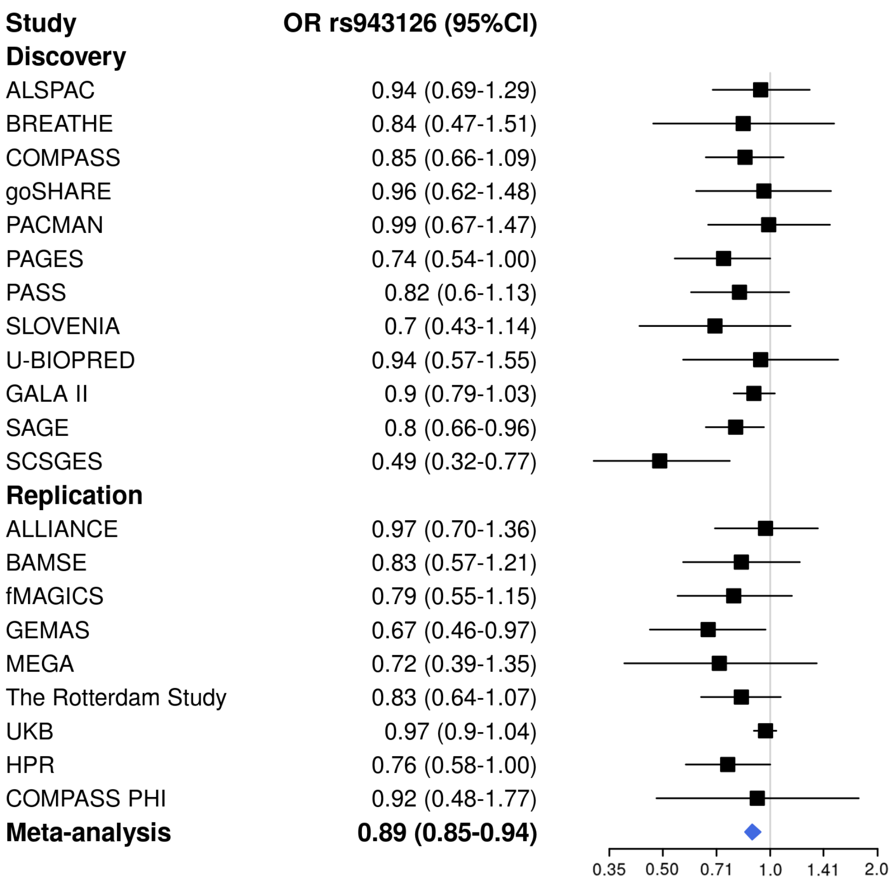

FIGURE 3 Forest plot of the association results for rs943126 (*PANK1*) in the meta-analysis of GWAS of asthma exacerbations. The subset of samples from BREATHE genotyped with the Illumina Infinium CoreExome-24 BeadChip (replication) had no available genotyped or imputed data for rs943126

TABLE 2 Sensitivity analysis for rs12091010 and rs943126 in individuals from the discovery stage

	Exacerbations in the last 6 months			Exacerbations in the last 12 months					
	European-descent populations			European-descent populations			Multi-ancestry meta-analysis		
rsID	OR (95% CI)	*p*	Cochran's Q *p*	OR (95% CI)	*p*	Cochran's Q *p*	OR (95% CI)	*p*	Cochran's Q *p*
rs12091010	0.84 (0.67–1.04)	1.08×10^{-1}	5.14×10^{-1}	0.86 (0.72–1.03)	9.13×10^{-2}	6.25×10^{-1}	0.82 (0.74–0.90)	3.45×10^{-5}	4.84×10^{-1}
rs943126	0.78 (0.64–0.96)	2.13×10^{-2}	8.61×10^{-1}	0.88 (0.74–1.04)	1.26×10^{-1}	8.28×10^{-1}	0.85 (0.78–0.93)	3.29×10^{-4}	7.50×10^{-2}

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; *p*, *p*-value.

TABLE 3 Results from the meQTL analysis in whole blood in the GALA II and SAGE studies for genome-wide significant hit in the discovery and two SNPs that were replicated

			Mexican Americans			Puerto Ricans			African Americans			Meta-analysis				
SNP-CpG pair	Position (hg19)	Closest genes	Coef	SE	*p*	Coef	SE	*p*	Coef	SE	*p*	Coef	SE	*p*	Cochran's Q *p*	Storey *q*
rs943126-cg26800131	91574784	*KIF20B*	−0.21	0.11	**2.99E-04**	−0.07	0.04	6.99E-02	−0.07	0.04	8.87E-02	−0.18	0.10	**1.85E-06**	4.45E−03	**9.95E-04**
rs943126-cg14920044	91296311	*SLC16A12*	0.09	0.05	9.77E-02	0.24	0.06	**1.68E-05**	0.12	0.06	**4.68E-02**	0.15	0.03	**4.61E-06**	1.24E-01	**1.24E-03**
rs943126-cg20654695	91444521	*KIF20B/PANK1*	−0.10	0.08	2.12E-01	−0.06	0.04	9.04E-02	−0.15	0.03	**2.04E-05**	−0.10	0.02	**9.96E-06**	1.98E−01	**1.79E-03**
rs943126-cg25770176	91405685	*PANK1*	−0.09	0.03	**1.43E-03**	0.00	0.09	2.78E-01	−0.07	0.02	**3.00E-03**	−0.07	0.02	**1.86E-05**	1.49E−01	**2.50E-03**
rs12091010-cg05612904	101491636	*DPH5*	−0.07	0.04	6.99E-02	−0.21	0.11	**2.99E-04**	−0.09	0.04	**2.72E-02**	−0.10	0.02	**2.31E-05**	9.52E−02	**1.20E-02**
rs943126-cg00475140	91404454	*PANK1*	−0.21	0.07	**1.39E-03**	−0.13	0.08	1.05E-01	−0.19	0.09	**3.19E-02**	−0.18	0.04	**4.28E-05**	5.25E−01	**4.60E-03**
rs943126-cg15620114	91296457	*SLC16A12*	0.09	0.08	2.64E-01	0.27	0.09	**3.87E-03**	0.20	0.08	**7.76E-03**	0.18	0.05	**1.53E-04**	5.70E−01	**1.32E-02**
rs943126-cg04957662	91411382	*KIF20B/PANK1*	−0.34	0.79	6.69E-01	−1.16	0.29	**1.33E-04**	−0.77	0.26	**2.89E-03**	−1.02	0.27	**1.72E-04**	3.14E−01	**1.32E-02**

Abbreviations: Coef, Coefficient of the regression; *p*, *p*-value; SE, standard error; Storey *q*, Storey *q*-value. Bold numbers corresponds to values less than .05 for both Storey *q* and *p*.

N-acetylglucosamine to the glycosaminoglycan-protein linkage region.[41] Decreased *EXTL2* causes an over-accumulation of GAGs[42] that can promote inflammation in injured areas.[43,44] Moreover, in bone marrow-derived macrophages from *EXTL2*$^{-/-}$ mice, there is overproduction of key molecules involved in inflammation and extracellular matrix remodeling, including tumor necrosis factor α (TNFα) and several matrix metalloproteinases.[43] In a scenario of overaccumulation of GAGs under the loss of *EXTL2* in macrophages, GAGs act as inflammatory mediators with strong Toll-like receptor 4 (TLR4) agonist capacity.[44] Interestingly, genetic variation in both *VCAM1* and *EXTL2* is associated with blood cell counts and multiple sclerosis, according to the GWAS catalog.[25]

PANK1 catalyzes coenzyme A biosynthesis, regulated by the transcription factor peroxisome proliferator-activating receptor α (PPAR-α),[45] a key anti-inflammatory factor in asthma.[46] A decrease in PPAR-α expression is accompanied by a decrease in the expression of PANK1 and miR-107, which is encoded within the intron 5 of *PANK1*. TLR4 can also downregulate miR-107. In turn, this leads to a higher cyclin-dependent kinase 6 (CDK6) expression and subsequently increases the adhesion of macrophages in response to LPS.[45] Bioproducts from bacterial infections, such as LPS, can trigger an inflammatory response and increase airway hyperresponsiveness and risk of asthma exacerbations.[47,48] Moreover, p53 can regulate cell cycle progression via upregulation of PANK1 after DNA damage[49] and metabolism.[50]

To prioritize gene targets, we assessed the functional capacity of relevant SNPs.[51] Both rs12091010 and rs943126 exhibited an association with DNA methylation at several nearby CpG sites in whole blood from African Americans and Hispanics/Latinos with asthma. Additionally, the SNPs rs12091010 and rs943126 were associated with *EXTL2* and *PANK1* gene expression in whole blood from Europeans. Specifically, the T allele of rs12091010, located at 6 kb downstream of the 3′ UTR of *VCAM1* and 150 kb upstream of the transcription start site of *EXTL2*, was associated with lower odds of having asthma exacerbations and decreased *EXTL2* expression[31] The T allele is more common among Latinos/Admixed Americans, followed by Europeans, Africans, and East Asians (Figure S6). The T allele of rs943126 at *PANK1*, which is less common among Europeans than the rest of populations (Figure S7), was associated with a higher risk of asthma exacerbations in the combined analysis of the discovery and replication phases and with decreased gene expression of *PANK1* in whole blood from Europeans according to PhenoScanner.[31] However, these eQTL effects were not validated in the GTEx data.[30]

In the discovery phase, the most significant association was located at the intronic SNP rs6888198 (*CDH12)*, but no evidence of replication was found in the second stage ($p > .05$) despite the consistency of the direction of the effect across study phases. Interestingly, rs6888198 showed variable MAF among populations, with the largest MAF among Africans and Latinos (Figure S8). *CDH12* has been associated with angiogenesis and progression of several types of cancers.[52–54] Specifically, in colorectal cancer, it has been suggested that *CDH12* increases cancer cell migration by promoting epithelial-mesenchymal transition via activation of the Snail transcription factor pathway. *CDH12* expression is positively modulated by the chemotactic factor *CCL2*,[53,54] whose levels increases in blood and airway smooth muscle from asthma patients compared to healthy controls.[55]

We also attempted to assess previously associated loci for asthma exacerbations or moderate-to-severe asthma for association with asthma exacerbations in multiple ethnic groups. Although several variants showed association at $p < .05$, none surpassed the stringent Bonferroni correction, which could be due to differences in study design, phenotype definition, ethnicity, and clinical characteristics, among others. Of note, none of the previous findings was initially described in Asian or African populations, which highlights the need to increase ethnic diversity in genomic studies of asthma exacerbations.

Our study has several limitations. First, the *VCAM1/EXTL2* and *PANK1* loci did not surpass a stringent Bonferroni threshold of 4.7×10^{-4} ($p = .05/106$ variants) in the replication stage nor the genome-wide significance in the combined analysis from all studies. Second, these loci exhibited modest effects sizes, which could impact the clinical relevance of these loci. Third, the history of asthma exacerbations was based on retrospective questionnaires in all cohorts but COMPASS, a randomized, prospective clinical trial. Fourth, to bring together large sample sizes necessary to map susceptibility variants, we considered studies where asthma exacerbations were reported for the previous 6 to 24 months or ever, which may have introduced some heterogeneity in the phenotype. Moreover, the replication stage comprised mostly European individuals, which hindered our capability to replicate associations driven in the discovery stage by non-Europeans. Despite these limitations, our findings exhibited consistent effects for the *VCAM1/EXTL2* and *PANK1* loci independent of the time period assessed. Future studies in adequately powered and phenotypically harmonized cohorts should untangle the role of these loci in the time-to-first exacerbation, the annual number of exacerbations, or the temporal distance among events, explore other epigenetic mechanisms known to be involved in asthma (e.g., histone modifications or miRNAs),[56] and the biological function of these genes. Moreover, although asthma exacerbation risk is influenced by sex in an age-dependent manner,[57] and our analyses were corrected for sex, future genome-wide gene-by-sex interaction scans may reveal the influence of sex on the genetic susceptibility to exacerbations. On the other hand, we acknowledge several study strengths. First, we leveraged clinical and genetic data from 46,947 asthma patients from different ethnicities from 18 independent studies. Our study had statistical power ≥80% to detect associations with MAF > 17% and relative risk (RR) >1.20 in the discovery stage and for variants with MAF ≥ 1%, and was powered at 80% to detect associations with larger effect sizes (RR ≥ 1.85). Second, we identified novel, biologically plausible genetic factors of asthma exacerbations demonstrated by transcriptomics and epigenomics studies and evidence for prior literature. Moreover, we accounted for blood cell-type heterogeneity to overcome the limitations of analyzing mixed cell types tissues.[56,58] Third, we evaluated previous genetic signals from asthma exacerbations in populations from several ancestries.

We identified suggestive loci for asthma exacerbations with consistent genetic effects across individuals from varying ancestral backgrounds using a multi-ancestry approach. We also demonstrated that these loci are biologically functional and regulate RNA expression and adjacent CpG site DNA methylation as meQTL in whole blood cells. Our findings highlight *VCAM1*, *EXTL2*, and *PANK1* as functional loci for asthma exacerbations applicable to people across different ancestral backgrounds, warranting future investigation of these novel genomic mechanisms underlying asthma exacerbations.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

All data necessary to evaluate the conclusions of this manuscript are reported in the main text and/or the Appendix S1. Genome-wide genotyping data for GALA II and SAGE are available at the database of Genotypes and Phenotypes (dbGaP) (Study Accession phs001274.v2.p1 and phs000092.v1.p1, respectively). The summary statistics of the multi-ancestry discovery phase are available at the Zenodo repository: 10.5281/zenodo.5513443.

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SUPPORTING INFORMATION

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