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Original research

Admixture mapping of severe asthma exacerbations in Hispanic/Latino children and youth

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ABSTRACT

Background In the USA, genetically admixed populations have the highest asthma prevalence and severe asthma exacerbations rates. This could be explained not only by environmental factors but also by genetic variants that exert ethnic-specific effects. However, no admixture mapping has been performed for severe asthma exacerbations.

Objective We sought to identify genetic variants associated with severe asthma exacerbations in Hispanic/Latino subgroups by means of admixture mapping analyses and fine mapping, and to assess their transferability to other populations and potential functional roles.

Methods We performed an admixture mapping in 1124 Puerto Rican and 625 Mexican American children with asthma. Fine-mapping of the significant peaks was performed via allelic testing of common and rare variants. We performed replication across Hispanic/Latino subgroups, and the transferability to non-Hispanic/Latino populations was assessed in 1001 African Americans, 1250 Singaporeans and 941 Europeans with asthma. The effects of the variants on gene expression and DNA methylation from whole blood were also evaluated in participants with asthma and in silico with data obtained through public databases.

Results Genomewide significant associations of Indigenous American ancestry with severe asthma exacerbations were found at 5q32 in Mexican Americans as well as at 13q13-q13.2 and 3p13 in Puerto Ricans. The single nucleotide polymorphism (SNP) rs1144986 (*C5orf46*) showed consistent effects for severe asthma exacerbations across Hispanic/Latino subgroups, but it was not validated in non-Hispanics/Latinos. This SNP was associated with *DPYSL3* DNA methylation and *SCGB3A2* gene expression levels.

Conclusions Admixture mapping study of asthma exacerbations revealed a novel locus that exhibited Hispanic/Latino-specific effects and regulated *DPYSL3* and *SCGB3A2*.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Admixed minorities in the USA, including Hispanic/Latino subgroups, show disproportionate rates of asthma and asthma exacerbations compared with European-descent populations, but no study has assessed the contribution of genetic variation to asthma exacerbations by admixture mapping.

WHAT THIS STUDY ADDS

⇒ Admixture mapping analysis of severe asthma exacerbations in Hispanics/Latinos revealed a functional genetic variant with ethnic-specific effect over two biologically plausibly genes implicated in this trait (DPYSL3 and SCGB3A2).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings have prioritised novel gene targets for future research in asthma.

INTRODUCTION

Asthma is a chronic inflammatory disease that shows remarkable heterogeneity by ethnicity and may result from the complex interplay between environmental, behavioural and genetic factors.[1] In fact, genetic ancestry is a critical factor for asthma susceptibility.[2] In the USA, asthma prevalence is the highest in Puerto Ricans (14.0%), followed by African Americans (10.7%), and the lowest in Mexican Americans (5.4%) and Asian Americans (4.5%).[3] However, racial/ethnic disparities are not limited to asthma prevalence, since Puerto Ricans and African Americans also show the highest

rates of asthma-related emergency room or urgent care visits.[4] Asthma exacerbations, defined as those events requiring urgent asthma care, hospitalisations or administration of systemic corticosteroids, contribute to the large healthcare expenditures of asthma[5] and asthma-related deaths.[6] Moreover, exacerbations impair individuals' quality of life[7] and long-term lung function.[8] Although environmental exposures, such as viral infections or air pollution, are known triggers for asthma exacerbations, several genetic loci for asthma exacerbations have been successfully uncovered through genomewide association studies in Hispanic/Latino populations.[9–11]

Hispanics/Latinos are American admixed individuals with variable influences from Indigenous American, African and European populations (ie, African ancestry is higher in Puerto Ricans, whereas Indigenous American ancestry is higher in Mexicans).[12] In a scenario where a trait shows differential rates in admixed individuals, admixture mapping in the most affected populations can identify genetic variants associated with that trait. In fact, mapping causal variants by long-range linkage disequilibrium decreases multiple testing burden and can be coupled with functional approaches to prioritise genetic variants that could have population-specific effects.

Given the disparities in asthma prevalence and outcomes, multiple studies have leveraged locus-specific genetic ancestry to identify genetic variants associated with asthma-related outcomes.[12–15] However, no admixture mapping of severe asthma exacerbations has been performed to date. We hypothesised that genetic variation might partially explain the ethnic differences in severe asthma exacerbations among Hispanics/Latinos. Hence, we aimed to identify novel genetic variants associated with severe asthma exacerbations by admixture mapping in Hispanic/Latino children and youth with asthma. We then sought to evaluate the potential functional consequences of those genetic variants and attempted to validate them in non-Hispanic/Latino populations.

METHODS

A full description of the methods with a graphical summary of the workflow (online supplemental figure E1) is found in online supplemental material.

Discovery population

We analysed genotypes from Puerto Ricans (n=1124) and Mexican Americans (n=625) from the study of Genes-Environment and Admixture in Latino Americans (GALA II), a case–control study of asthma in Hispanics/Latinos aged 8–21 years old recruited in the USA and Puerto Rico between 2006 and 2014. GALA II was approved by the Human Research Protection Program Institutional Review Board of the University of California, San Francisco (USA), and participants/parents provided written assent/consent, respectively. Participants were eligible if they reported four Hispanic/Latino grandparents. Asthma cases were diagnosed by a physician, had asthma symptoms and reported use of controller or rescue medication in the 2 years preceding enrolment.[16] Severe asthma exacerbations were defined as the presence of any of the following events in the past 12 months: use of oral corticosteroids, asthma-related hospitalisations or unscheduled asthma care.[17] Treatment category, defined following the Expert Panel Report 3 (EPR-3) guidelines for the diagnosis and management of asthma,[18] was used as a proxy for asthma severity. Three levels were defined based on the use of short beta-agonists (step 1); one inhaled corticosteroid, leukotriene inhibitor or theophylline tablet (step 2); or more than one or a combination of an inhaled corticosteroid, leukotriene inhibitor; or theophylline tablet or a combination of inhaled corticosteroids and long-beta agonists (step 3).

Whole-genome sequencing data generation and processing

Whole-genome sequencing (WGS) was conducted on a HiSeq X system (Illumina, San Diego, California). Data generation and quality control (QC) are described in online supplemental material. Genotypes used in this study were based on TOPMed freeze 8 data.

Local and global ancestry estimation

The ancestral reference panel for ancestry estimation included 90 HapMap phase II Europeans (CEU), 90 Africans (YRI) and 71 Native Americans (NAM).[19] Local ancestry was estimated with RFMIX V.2[20] based on biallelic single nucleotide polymorphisms (SNPs) that passed the QC procedures of the WGS pipeline and that overlapped with the reference panel (402 838 SNPs). Global ancestry was calculated as the genomewide average of local ancestry.

Admixture mapping in Hispanics/Latinos

The association of asthma exacerbations and the number of copies of African, European and Indigenous American local ancestry (0, 1 or 2 copies) at each SNP analysed was tested separately in Hispanic/Latino subgroups. This was performed through logistic regression models with correction for global ancestry, age, sex and treatment category (as a proxy for asthma severity). To account for multiple comparison testing, the final effective number of tests was defined as the sum of the two largest effective numbers of ancestry blocks, consistent with Horimoto *et al*[21], and as detailed in online supplemental material.

Fine-mapping and replication

Fine-mapping of variants with minor allele frequency (MAF) ≥1% within the genomewide significant admixture mapping peaks was performed with correction for the same covariates used in the admixture mapping. To correct for multiple comparison, an adjusted threshold of significance was defined as $p \leq 0.05$/number of effective tests. To evaluate whether independent SNPs account for the admixture mapping signal, we performed stepwise conditional regression analyses adjusting the association of local ancestry by the allele dosage of associated SNPs. Interaction of local ancestry on the association of the SNPs with exacerbations was evaluated in a regression model including the same covariates as in the main model with an interaction term SNP × local ancestry.

Peakwise independent significant SNPs identified in Mexican Americans were replicated in Puerto Ricans, and those identified in Puerto Ricans were assessed in Mexican Americans. Additional validation was sought in non-Hispanic/Latino participants with asthma, including 1101 African Americans from the Study of African Americans, Asthma, Genes and Environments, 1250 Singaporean Chinese from the Singapore Cross Sectional Genetic Epidemiology Study and 941 Europeans from several studies: the MEchanism underlying the Genesis and evolution of Asthma study, the Genomics and Metagenomics of Asthma Severity study, the Children, Allergy, Milieu, Stockholm, Epidemiology study and the Infancia and Medio Ambiente study. Details of studies included in the replication are described in online supplemental material and online supplemental table E1.

Fine-mapping of rare variants (MAF <1%) was conducted using the SKAT-O test[22] analysing 1-kilobase (kb) sliding

windows with 500 bp increments within the admixture mapping peak limits. The threshold of significance was defined based on Storey q[23] <0.05.

Methylation profiling and QC

DNA methylation from whole blood was profiled using the Illumina Infinium HumanMethylation450 BeadChip or the Infinium EPIC BeadChip arrays. QC is detailed in online supplemental material. Briefly, low-quality probes and samples, outliers of DNA methylation and samples with sex discordance or mixed genotype distributions on the control SNP probes were excluded. Standard background correction, dye-bias correction, interarray normalisation, and probe-type bias adjustment were conducted, and beta values were transformed to M-values.

RNA sample processing, sequencing and QC

Total RNA was quantified using the Quant-iT RiboGreen RNA Assay Kit and normalised for library preparation with the Illumina TruSeq Stranded mRNA Sample Preparation Kit. Libraries were sequenced according to the manufacturer's protocols using the HiSeq 4000 system (Illumina). Sample processing and QC are detailed in online supplemental material. Expression values were normalised across samples using an inverse normal transformation.

Functional assessment of associated SNPs

Quantitative trait loci (QTL) analyses in data from whole blood were conducted separately in Mexican American and Puerto Rican participants with asthma from GALA II for those CpG sites or genes with a transcription start site located within 1 Mb of the significant SNPs. Linear regression models were adjusted for exacerbations status, age, sex, treatment category, and genetic ancestry. *Cis-e*xpression QTL (eQTL) analyses were adjusted by the top 60 PEER factors,[24] and *cis*-methylation QTL (meQTL) models by cell-type heterogeneity and methylation batch. The population sub-group results were then meta-analysed. In silico evidence of functional effects of the variant on gene expression and DNA methylation was assessed using the Genotype-Tissue Expression (GTEx) V.8 Portal,[25] PhenoScanner V.2,[26] Open Targets Genetics[27], and the Genetics of DNA Methylation Consortium (GoDMC).[28] Chromatin interactions were determined using CHiCP.[29] Gene expression was inspected using the GTEx Portal[25] and REALGAR.[30]

RESULTS

Discovery sample characteristics

A total of 820 out of 1124 Puerto Ricans had exacerbations in the last 12 months (72.9%), while 223 out of 625 Mexican Americans reported exacerbations for the same period (35.7%). Most of the exacerbators among Puerto Ricans and non-exacerbators among both ethnic subgroups were in the lowest treatment category, while the distribution in Mexican American exacerbators was more balanced. Moreover, no significant differences in global ancestry were detected between exacerbators and non-exacerbators ($p>0.05$) (table 1).

Stratified admixture mapping

Genomewide significant associations were found between Indigenous American ancestry and severe asthma exacerbations at chromosomes 3p13 and 13q13.2 in Puerto Ricans (table 2, figure 1A, online supplemental figure E2 in online supplemental material) ($p\leq4.33\times10^{-5}$, accounting for 1154 ancestry blocks). The most significant association at chromosome 3p13 corresponded to rs4677148, where Indigenous American ancestry was associated with lower odds of exacerbations (OR: 0.57, 95% CI 0.44 to 0.74, $p=2.55\times10^{-5}$), while European ancestry was associated with a higher odds of having exacerbations (OR: 1.40, 95% CI 01.16 to 1.94, $p=1.82\times10^{-3}$) but no significant association with African ancestry was detected ($p>0.05$). The strongest association with the odds of severe exacerbations at 13q13.2 was located at rs10514839 (OR: 2.18, 95% CI 1.55 to 3.06, $p=6.56\times10^{-6}$), whereby European or African ancestry showed no association.

Among Mexican Americans, we identified one admixture mapping peak at chromosome 5q32, whereby Indigenous American ancestry was genomewide significantly associated with the odds of severe exacerbations ($p\leq4.51\times10^{-5}$, accounting for 1107 ancestry blocks) (table 2, figure 1B, online supplemental figure E3). The most significant association in the region was located at rs10477350, where Indigenous American ancestry was associated with greater odds of exacerbations (OR: 1.73, 95% CI

Table 1 Characteristics of the asthma participants recruited between 2006 and 2014 for the Genes-Environments and Admixture in Latino Asthmatics (GALA II) study and included in the current study

	Puerto Ricans (N=1124)			Mexican Americans (N=625)		
	Exacerbators	Non-exacerbators	P value	Exacerbators	Non exacerbators	P value
Number of individuals	820	304		223	402	
Sex (% male)	443 (54.0)	160 (52.6)	7.27×10^{-1}	129 (57.8)	226 (56.2)	7.57×10^{-1}
Age, mean+SD (years)	12.2±3.2	13.8±3.6	1.83×10^{-11}	12.2±3.2	13.2±3.4	6.16×10^{-4}
European ancestry, mean±SD (%)	62.6±10.7	63.2±10.5	5.45×10^{-1}	38.6±14.7	40.0±13.5	3.03×10^{-1}
African ancestry, mean±SD (%)	23.5±11.7	26.7±11.4	1.57×10^{-1}	4.6±2.2	5.0±3.3	3.03×10^{-1}
Indigenous American ancestry, mean±SD (%)	13.8±3.93	14.3±4.8	1.16×10^{-1}	56.7±15.2	55.0±14.2	2.00×10^{-1}
Treatment category, n (%)						
Step 1	353 (43.0)	227 (74.7)	8.27×10^{-21}	53 (23.7)	185 (46.0)	6.57×10^{-8}
Step 2	239 (29.1)	41 (13.5)	1.07×10^{-7}	86 (38.6)	131 (32.6)	1.57×10^{-1}
Step 3	228 (27.9)	36 (11.8)	3.23×10^{-8}	84 (37.7)	86 (21.4)	1.82×10^{-5}

For continuous variables, the mean and SD are displayed, and Mann-Whitney-Wilcoxon test was applied for the comparison of exacerbators versus non-exacerbators. For categorical variables, the number and proportion of subjects in each category are shown and a χ^2 test was applied for the comparison of exacerbators versus non-exacerbators.

Table 2 Significant admixture mapping peaks identified in Mexican Americans and Puerto Ricans from GALA II (2006–2014)

Ethnicity/ancestry	Chr. band	Start (Bp)*	End (Bp)*	Peak size (Kb)	rsID†	OR (95% CI)	P value
Puerto Rican/Indigenous American	3p13	72 283 579	72 585 953	302	rs4677148	0.57 (0.44 to 0.74)	2.55×10^{-5}
	13q13.2	34 471 415	35 919 337	1448	rs10514839	2.18 (1.55 to 3.06)	6.56×10^{-6}
Mexican American/Indigenous American	5q32	147 809 331	147 911 637	102	rs10477350	1.73 (1.34 to 2.24)	3.23×10^{-5}

*Coordinates are referred to the human reference genome assembly GRCh38.
†Genetic variant with the minimum association p value within the peak.
Bp, base pairs; Chr, chromosome; iSNPs, independent single nucleotide polymorphisms; Kb, kilobases; rsID, reference single nucleotide polymorphism identifier.

1.34 to 2.24, $p=3.23\times10^{-5}$) and European ancestry with lower odds (OR: 0.60, 95% CI 0.46 to 0.78, $p=1.46\times10^{-4}$).

No genomewide significant associations were found between severe asthma exacerbations and African or European ancestry in both ethnic subgroups (online supplemental figure E4). Moreover, a meta-analysis of both ethnic subgroups did not yield any additional admixture mapping peak at genomewide significant level.

Fine-mapping analyses

We next performed fine mapping of common variants via allelic association testing (table 3, online supplemental table E2). We found a region in the admixture mapping peak at 5q32, where genetic variation was significantly associated with severe asthma exacerbations in Mexican Americans after accounting for the number of variants tested within the peak. Specifically, four independent variants were associated with severe exacerbations (figure 2A). The minor alleles of SNPs rs1144986 (*C5orf46*) and rs35439318 (*SCGB3A2/CTC-327F10.1*) were associated with lower odds of having exacerbations: OR for G allele: 0.43, 95% CI 0.28 to 0.66, $p=9.45\times10^{-5}$ and OR for C allele: 0.51, 95% CI 0.34 to 0.74, $p=5.26\times10^{-4}$, respectively. Moreover, the A alleles of rs7704889 (*C5orf46/EEF1GP2*) and rs10035432 (*SCGB3A2/CTC-327F10.1*) were associated with higher odds of exacerbations: OR: 1.58, 95% CI 1.23 to 2.11, $p=4.00\times10^{-4}$ and OR: 1.61, 95% CI 1.23 to 2.11, $p=4.82\times10^{-4}$, respectively. No significant associations were detected in any of the regions in Puerto Ricans.

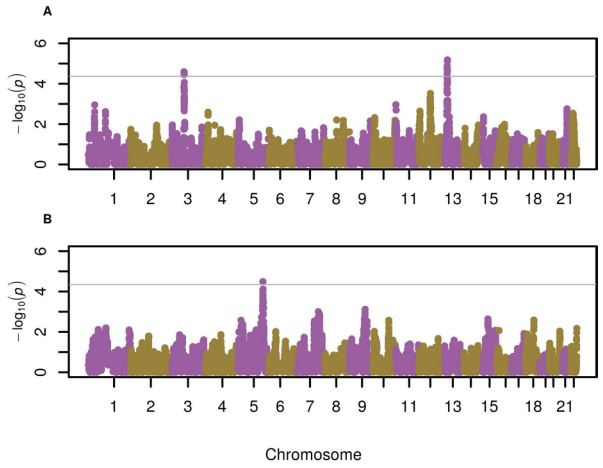

Figure 1 Manhattan plot for the admixture mapping results of severe exacerbations in participants with asthma from GALA II (2006–2014). (A) Association results for Indigenous American ancestry in Puerto Ricans. (B) Association results for Indigenous American ancestry in Mexican Americans. The association with local ancestry is represented as $-\log_{10}$ p value on the *y*-axis along the chromosomes (*x*-axis). The threshold for significance (grey line) was defined as p<0.05/sum of the two largest values for the effective number of ancestry blocks: $p\leq4.33\times10^{-5}$ in Puerto Ricans, accounting for 1154 ancestry blocks (African: 560, European: 594, Native American: 432); and $p\leq4.51\times10^{-5}$ in Mexican Americans, accounting for 1107 ancestry blocks (African: 637, European: 470, Native American: 431).

The stepwise addition of the independent SNPs as covariates to the regression model that tested the association of the lead ancestry SNP with severe asthma exacerbations revealed that the SNPs accounted for the 5q32 peak since the association of local ancestry became non-significant (online supplemental table E3). Moreover, the association of the SNPs revealed by fine-mapping and severe exacerbations remained significant after additional adjustment by local ancestry, and no significant interaction with local ancestry was found (online supplemental table E4). To assess the robustness of the associations to socioeconomic and clinical factors, we performed sensitivity analyses with adjustment by secondhand smoking exposure, insurance status, income quartile, maternal education and obesity, confirming that the effects were not explained by these factors (online supplemental table E5).

We next assessed whether the independent variant replicated among Hispanics/Latino subgroups. In Puerto Ricans, the SNP rs1144986 (OR for G allele: 0.79, 95% CI 0.62 to 1.00, $p=4.94\times10^{-2}$) had consistent effects compared with Mexican Americans. In the meta-analysis of Hispanics/Latinos, the G allele of rs1144986 showed a protective effect over exacerbations (OR: 0.60, 95% CI 0.33 to 1.08, $p=1.61\times10^{-4}$, Cochran's Q $p=1.40\times10^{-2}$). Moreover, an analysis in 1462 Mexican Americans and 2346 Puerto Ricans revealed that this SNP was not associated with the underlying asthma susceptibility at p<0.05 (online supplemental table E6).

The SNP that showed significant and consistent effects in Hispanic/Latino subgroups (rs1144986) was assessed for validation in non-Hispanic/Latino populations. However, no association was found with severe exacerbations (p>0.05) in Singaporean Chinese, African Americans or Spanish individuals, or with less severe exacerbations, including school absences in 421 Swedish children or wheezing in the last year in 100 Spanish individuals (online supplemental table E7).

We next tested the association of rare variants with severe asthma exacerbations. No significant associations were found within the admixture mapping peaks identified in either Puerto Ricans or Mexican Americans ($q>0.05$).

Assessment of functional effects of the genetic variants

The effect of rs1144986 on DNA methylation in whole blood from Hispanic/Latino participants with asthma was evaluated for 196 CpG sites located within ±1 Megabase (Mb) of the SNP. The SNP rs1144986 was significantly associated with three probes annotated to *DPYSL3*, being cg04833034, at 57.4 kb of *DPYSL3*, the most significant CpG ($p=5.17\times10^{-6}$, $q=3.41\times10^{-3}$). Moreover, associations for CpGs at *PPP2R2B*

Table 3 Association results of independent genetic variants at chromosome 5 that were peak-wise significantly associated with severe asthma exacerbations in Hispanics/Latinos from GALA II (2006–2014)

rsID	Position (Bp)*	A1/A2	Closest gene	Mexican Americans			Puerto Ricans			Meta-analysis	
				EAF	OR (95% CI)	P value	EAF	OR (95% CI)	p value	OR (95% CI)	P value
rs1144986	147 883 415	G/A	*C5orf46*	0.13	0.43 (0.28 to 0.66)	**9.45×10^{-5}**	0.22	0.79 (0.62 to 1.00)	**4.94×10^{-2}**	0.60 (0.33 to 1.08)	**1.61×10^{-4}†**
rs7704889	147 911 637	A/G	*C5orf46/EEF1GP2*	0.54	1.58 (1.23 to 2.03)	**4.00×10^{-4}**	0.42	0.97 (0.79 to 1.20)	7.94×10^{-1}	1.23 (0.77 to 1.98)	**6.57×10^{-3}†**
rs10035432	147 855 193	A/G	*SCGB3A2/CTC-327F10.1*	0.26	1.61 (1.23 to 2.11)	**4.82×10^{-4}**	0.21	1.02 (0.81 to 1.29)	8.72×10^{-1}	1.28 (0.81 to 2.00)	**5.93×10^{-3}†**
rs35439318	147 862 111	C/T	*SCGB3A2/CTC-327F10.1*	0.15	0.51 (0.34 to 0.74)	**5.26×10^{-4}**	0.22	0.83 (0.65 to 1.05)	1.27×10^{-1}	0.66 (0.41 to 1.08)	**1.45×10^{-3}†**

Association p values<0.05 are shown in bold.
*Coordinates are referred to the human reference genome assembly GRCh38.
†A random effect model was applied since heterogeneity was found between populations (Cochran's Q p value<0.05).
A1, effect allele; A2, non-effect allele; Bp, base pairs; EAF, effect allele frequency; rsID, reference single nucleotide polymorphism identifier.

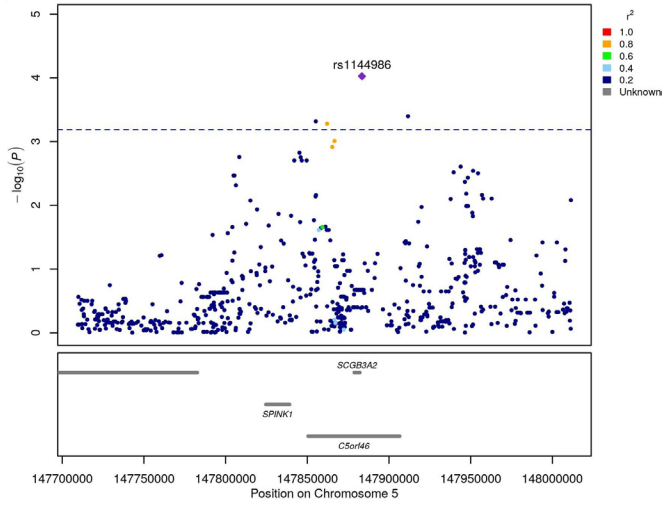

Figure 2 Locus zoom for the fine-mapping results displaying the region around the most significant signals at 5q32 in Mexican Americans with asthma from GALA II (2006–2014). The statistical significance of association results ($-\log_{10}$ p value) is represented for each single nucleotide polymorphism (SNP) as a dot (left *y*-axis) by chromosome position (*x*-axis). SNPs are colour-coded to show their linkage disequilibrium (LD) with the most significant SNP based on the pairwise r^2 values from Mexican Americans. The peak-wise significance threshold is represented as a dashed blue line.

and *C5orf46* were also observed (table 4). Notably, the associations with cg24686270 and cg10930901 were replicated in the GoDMC results[28] ($p=1.1\times10^{-139}$ and 7.1×10^{-29}, respectively). *DPYSL3* expression in bronchial epithelial cells was found to be increased in severe asthma in publicly available gene expression data sets of asthma participants (online supplemental figure E5). Additionally, the meQTL rs1144986 showed evidence of chromatin interaction with *C5orf46* in lymphoblastoid cells (CHiCAGO score=11.7) and association with H3K4me1 histone marks in blood (online supplemental table E4). Notably, none of the significant CpGs regulated the expression of nearby genes in whole blood in a subset of 126 Puerto Ricans and 40 Mexicans with DNA methylation and gene expression data available at a false discovery rate-adjusted p<0.05 (online supplemental table E8).

The effect of rs1144986 over the expression of genes with transcription start site within ±1 Mb was assessed. From the 5 SNP-gene pairs, the SNP rs1144986 showed significant associations with gene expression of *SCGB3A2* at $q<0.05$ in whole blood ($p=6.62\times10^{-22}$; $q=6.62\times10^{-20}$), and the association was also validated in blood according to the GTEx ($p=5.1\times10^{-10}$),[25] PhenoScanner and Open Targets Genetics (minimum $p=3.3\times10^{-310}$).[26 27]

Discussion

This admixture mapping analysis of severe asthma exacerbations in Hispanic/Latino children with asthma identified several genomic regions in which local Indigenous American or European ancestry was associated with severe asthma exacerbations in Puerto Ricans and Mexican Americans. Although fine mapping in Puerto Ricans revealed no significant variants, we found four independent SNPs explaining the admixture mapping peak for Indigenous American ancestry at chromosome 5q32 in Mexican Americans, including rs1144986 (*C5orf46*), which showed significant consistent effects among Hispanic/

Table 4 Significant results from the QTL mapping in Hispanics/Latinos from GALA II (2006–2014)

SNP analysis	Target	Position†	Gene	Puerto Ricans			Mexican Americans			Meta-analysis*		
				Coef (SE)	P value	PQ	Coef (SE)	P value	PQ	Coef (SE)	P value	Q
rs1144986 -meQTL	cg04833034	147452619	*DPYSL3*	0.18 (0.04)	1.58×10^{-5}	0.66	0.11 (0.07)	1.28×10^{-1}	NA‡	0.16 (0.04)	6.36×10^{-6}	8.13×10^{-4}
	cg09639133	147451646	*DPYSL3*	0.22 (0.05)	5.10×10^{-5}	0.53	0.14 (0.07)	5.25×10^{-2}	NA‡	0.19 (0.04)	1.13×10^{-5}	8.13×10^{-4}
	cg10930901	147505871	*DPYSL3*	−0.18 (0.05)	7.96×10^{-5}	0.26	−0.05 (0.07)	4.56×10^{-1}	NA‡	−0.14 (0.04)	1.84×10^{-4}	8.79×10^{-3}
	cg01112778	147081424	*PPP2R2B*	0.14 (0.05)	4.41×10^{-3}	0.53	0.17 (0.09)	5.29×10^{-2}	NA‡	0.15 (0.04)	5.56×10^{-4}	2.03×10^{-2}
	cg24686270	147901750	*C5orf46*	0.10 (0.03)	4.25×10^{-3}	0.47	0.10 (0.06)	1.21×10^{-1}	NA‡	0.10 (0.04)	1.04×10^{-4}	2.98×10^{-2}
rs1144986 - eQTL	ENSG00000164265	147870682	*SCGB3A2*	0.68 (0.08)	1.01×10^{-15}	NA	0.47 (0.10)	1.85×10^{-6}	NA	0.60 (0.06)	6.12×10^{-21}	3.06×10^{-20}

*A fixed effect model was applied since no heterogeneity was found between populations (Cochran's Q p value>0.05).
†Chromosomal positions referred to the genome assembly GRCh38. For CpG sites, the location of the CpG is stated. For genes, the location of the transcription start site is shown.
‡The SNP did not meet the genotype inclusion criteria for the individuals profiled with the EPIC array.
Coef, regression coefficient estimate; NA, not available/applicable; PQ, Cochran's Q-test p value; Q, Q-value; SE, standard error of the regression coefficient estimate.

Figure 3 Gene expression levels of *SCGB3A2* in whole blood by genotype at rs1144986 in participants with asthma from GALA II (2006–2014). (A) Mexican Americans and (B) Puerto Ricans.

Latino subgroups. Interestingly, none of the four loci was associated with asthma exacerbations in non-Hispanic/Latino populations, suggesting ethnic-specific effects shared among Hispanic/Latino subgroups. This could be explained, at least partially, due to differences in allele frequency and ethnic background. For example, at 5q32, Indigenous American ancestry was associated with higher odds of exacerbations in Mexican Americans, and the risk allele (A) of rs1144986 was more common among Native Americans (frequency=98%) and Mexicans (frequency=87%) than in Puerto Ricans (frequency=78%) or Europeans (frequency=67%) (online supplemental table E4, E6). The fact that Indigenous American ancestry is around 2% in African Americans,[31] which could contribute to the lack of validation of these genetic variants despite the higher risk allele frequency (89%) observed.

An analysis of functional effects revealed that rs1144986 altered DNA methylation of several nearby genes, including *DPYSL3*. The protein DPYSL3 is involved in cytoskeleton remodelling by participating in the signalling of class 3 semaphorins. While the role of *DPYSL3* in asthma is unclear, it is coexpressed with genes involved in airway type 2 inflammation.[32] However, *DPYSL3* expression in whole blood data from Hispanics/Latinos could not be evaluated due to low levels or lack of expression, consistently with the GTEx data.[25] Additionally, the protective allele of rs1144986 increased *SCGB3A2* expression in blood (figure 3), although *SCGB3A2* is predominantly expressed in the lung.[25] *SCGB3A2* is involved in lung development[33] and has shown an anti-inflammatory role in mice.[34–37] More recently, the role of secretoglobins as airway immunoregulators is gaining interest.[38] Lung expression levels of proinflammatory cytokines, IL-4, IL-5 and IL-13, are lower in ovalbumin-induced mice pretreated with SCGB3A2 compared with those not treated with it.[36 37] Plasma *SCGB3A2* levels are decreased in severe asthma,[39] and *SCGB3A2* polymorphisms have been associated with asthma susceptibility.[40] In human bronchial epithelial cells, SCGB3A2 decreased airway inflammation inhibiting the extracellular signal-regulated kinase (ERK) and the c-Jun N-terminal kinase (JNK) activation.[41] In lung cancer, SCGB3A2 induced pyroptotic cell death. Interestingly, participants with higher *SCGB3A2* gene expression manifested higher survival rates.[42] Moreover, *SCGB3A2* shows antifibrotic activity through increased expression of STAT1

phosphorylation and *SMAD7* expression,[43 44] hence, decreasing SMAD2/3 phosphorylation, which attenuates the TGFβ signalling,[44] a key pathway implicated in airway remodelling,[45] allergic airway inflammation[46] and drug response in asthma.[47] Taken together, this evidence suggests that these genes may be involved in susceptibility to asthma exacerbations and merit further exploration to understand their specific role.

Our study has several strengths and limitations. We focused on minority populations at high risk of asthma that have undergone distinct historical processes and show differential asthma exacerbations rates. Although we identified several regions in which local ancestry was associated with severe exacerbations, analysing two different Hispanic/Latino subgroups may have hindered our power to detect associations. Specifically, this could have affected the identification of SNPs in the regions where Indigenous American ancestry was associated with exacerbations in Puerto Ricans, as this ancestral population has a smaller contribution to their genetic background compared with Mexican Americans. Our study was especially underpowered to detect an association of rare variants. Specifically, assuming 30% of causal risk variants, we were only powered at >80% to detect rare variant signals with a maximum OR ≥18 in Puerto Ricans, likely due to the larger sample size compared with Mexicans. Moreover, although genetic signals identified by fine-mapping exceeded the respective peakwise threshold of significance (table 2, online supplemental table E2), none would have exceeded a stringent correction for the total number of independent variants tested in the discovery stage ($p=0.05/1\ 977\ SNPs=2.53\times10^{-5}$). Furthermore, we also sought to determine whether these genetic variants may exert the same effects in non-Hispanic/Latino populations. The fact that none of the variants was validated in non-Hispanics/Latinos suggests that they could exhibit ethnic-specific effects. We attempted to overcome these limitations by performing functional analyses to reveal the effects of the variant identified on whole blood gene expression and DNA methylation in Hispanics/Latinos. Although whole blood epigenetic and transcriptional signals may capture the inflammatory component related to specific blood cell types, future studies in airway tissues should be required due to the modest cross-tissue replication described in asthma.[48] However, given that we analysed a mixed cell-type tissue, our analyses were adjusted by blood cell-type heterogeneity to overcome this limitation.[48] Despite this, other epigenetic mechanisms known to be involved in asthma (eg, histone modifications or miRNAs[49]) could also underlie the functional role of the genetic variation. Moreover, chromatin interactions were evaluated in silico using a publicly available database due to the lack of experimental data from Hispanic/Latino participants with asthma. Therefore, the role of these loci in asthma exacerbations should be explored in future studies using cell lines from asthma participants or animal models of this disease.

In summary, we leveraged local ancestry to identify genomic regions that contribute to severe asthma exacerbations in Hispanic/Latinos. Indigenous American ancestry was associated with asthma exacerbation risk at 5q32-q33.1 and novel association of a genetic variant with severe asthma exacerbations with a potential population-specific effect was uncovered. Moreover, these variants had functional effects on *SCGB3A2* gene expression and *DPYSL3* DNA methylation, two genes that are plausibly implicated in severe exacerbations.

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