Genetic analyses identify *GSDMB* associated with asthma severity, exacerbations, and antiviral pathways

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Background: The Chr17q12-21.2 region is the strongest and most consistently associated region with asthma susceptibility. The functional genes or single nucleotide polymorphisms (SNPs) are not obvious due to linkage disequilibrium.

Objectives: We sought to comprehensively investigate whole-genome sequence and RNA sequence from human bronchial epithelial cells to dissect functional genes/SNPs for asthma severity in the Severe Asthma Research Program.

Methods: Expression quantitative trait loci analysis (n = 114), correlation analysis (n = 156) of gene expression and asthma phenotypes, and pathway analysis were performed in bronchial epithelial cells and replicated. Genetic association for asthma severity (426 severe vs 531 nonsevere asthma) and longitudinal asthma exacerbations (n = 273) was performed.

Results: Multiple SNPs in gasdermin B (*GSDMB*) associated with asthma severity (odds ratio, >1.25) and longitudinal asthma exacerbations ($P < .05$). Expression quantitative trait loci analyses identified multiple SNPs associated with expression levels of post-GPI attachment to proteins 3, *GSDMB*, or gasdermin A ($3.1 \times 10^{-9} < P < 1.8 \times 10^{-4}$). Higher expression levels of *GSDMB* correlated with asthma and greater number of exacerbations ($P < .05$). Expression levels of *GSDMB* correlated with genes involved in IFN signaling, MHC class I antigen presentation, and immune system pathways (false-discovery rate–adjusted $P < .05$). rs1031458 and rs3902920 in *GSDMB* colocalized with IFN regulatory factor binding sites and associated with *GSDMB* expression, asthma severity, and asthma exacerbations ($P < .05$).

Conclusions: By using a unique set of gene expression data from lung cells obtained using bronchoscopy from comprehensively characterized subjects with asthma, we show that SNPs in *GSDMB* associated with asthma severity, exacerbations, and *GSDMB* expression levels. Furthermore, its expression levels correlated with asthma exacerbations and antiviral pathways.

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Thus, *GSDMB* is a functional gene for both asthma susceptibility and severity. (J Allergy Clin Immunol 2021;147:894-909.)

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Asthma is a common inflammatory airway disease. ORMDL sphingolipid biosynthesis regulator 3 (*ORMDL3*) in the chr17q12-21.2 region was the first gene identified through genome-wide association study (GWAS) of asthma.[1] Since then, GWAS, candidate gene replication, and gene expression studies have consistently identified or confirmed single nucleotide polymorphisms (SNPs) in multiple genes in this region that are associated with asthma susceptibility, including post-GPI attachment to proteins 3 (*PGAP3*),[2-4] *ERBB2*,[5] *IKZF3*,[6-9] *ZPBP2*,[10,11] gasdermin B (*GSDMB*),[1,5,8,12-20] *ORMDL3*,[11,21-25] and gasdermin A (*GSDMA*).[9,14,15,26] SNPs in *IKZF3*,[27] *ZPBP2*,[28] *GSDMB*,[10,29,30] and *PSMD3*[29] have also been associated with allergic responses. However, partially because of linkage disequilibrium (LD), it has been difficult to determine the specific genes or SNPs responsible for these associations. In addition, most published GWASs of asthma have tested the association of SNPs with asthma susceptibility (mild or severe asthma vs healthy controls), not asthma severity. To analyze asthma severity, we performed a genetic association analysis for severe asthma compared with nonsevere asthma and asthma exacerbations longitudinally over a 3-year period.

Autoimmune diseases (ADs) arise from abnormal immune responses to self-antigens. SNPs in *ERBB2*,[31] *IKZF3*,[32-44] *ZPBP2*,[28,45] *GSDMB*,[46-57] and *GSDMA*[58,59] have been associated with various ADs. In a previously published GWAS, we were the first to report that the opposite risk alleles in *IL13*, *TNIP1*, *HLA-DRA*, and *GSDMB* associated with asthma and AD.[60] In this study, we comprehensively compared all the GWAS-identified SNPs associated with asthma, allergy, and AD in the chr17q12-21 region to reveal genetic effects on the immunopathogenesis of asthma, allergy, and AD.

In a recent review, genetic association, expression quantitative trait loci (eQTL), and epigenetics of 17 SNPs in the chr17q12-21.2 region with asthma have been summarized.[61] Proximal (*PGAP3-ERBB2*), core (*IKZF3-ZPBP2-GSDMB-ORMDL3*), and distal (*GSDMA*) regions have been suggested as independent regions associated with asthma.[61]

To delineate the functional genes/SNPs for asthma severity in this region, we used a unique data set of lung gene expression data obtained from bronchial brushing during investigational bronchoscopy in extensively characterized patients with current asthma plus healthy controls. We hypothesize that combing SNP with RNA gene expression data from lung cells of patients with asthma, we will be able to determine the functional asthma genes/SNPs in this complicated chromosomal region.

Abbreviations used

AD:	Autoimmune disease
BEC:	Bronchial epithelial cell
eQTL:	Expression quantitative trait loci
GSDMA:	Gasdermin A
GSDMB:	Gasdermin B
GWAS:	Genome-wide association study
IRF:	IFN regulatory factor
LD:	Linkage disequilibrium
MAF:	Minor allele frequency
ORMDL3:	ORMDL sphingolipid biosynthesis regulator 3
PGAP3:	Post-GPI attachment to proteins 3
QC:	Quality control
RNAseq:	RNA sequence
SARP:	Severe Asthma Research Program
SNP:	Single nucleotide polymorphism
TOPMed:	Trans-Omics for Precision Medicine
T1D:	Type I diabetes
WGS:	Whole-genome sequencing

METHODS

Study subjects

Severe Asthma Research Program (SARP) is a currently active multicenter program funded for the last 18 years by the National Heart, Lung, and Blood Institute. Subjects with mild to severe asthma (enriched for severe) and a subset of controls have been extensively studied using standardized protocols. The earlier SARP cohort was cross-sectional (n = 1644). In a subset of subjects with mild to severe asthma, RNA was isolated from epithelial cells (bronchial epithelial cells [BECs]; n = 155), which were obtained from brush biopsies (Table I; see Table E1 in this article's Online Repository at www.jacionline.org).[62-64] The current SARP cohort is an ongoing longitudinal study (n = 714).[65-67] Bronchoscopy was performed on a subset of the longitudinal cohort to obtain epithelial cells from brush biopsies (n = 156) for RNA sequence (RNAseq) (Table I and Table E1). All studies were approved by the appropriate institutional review board at the participating sites including informed consent.

Statistical analysis

Selection of SNPs and RNAseq data. Whole-genome sequencing (WGS) in SARP (n = 1888; version Freeze 6; dbGaP accession: phs001446) was performed through NHLBI-sponsored Trans-Omics for Precision Medicine (TOPMed) Program (www.nhlbiwgs.org). Standard quality control (QC) was performed. All SNPs in the chr17q12-21.2 region were extracted (hg38: *PPP1R1B* to *CSF3*; chr17:39,626,924-40,017,813) in the longitudinal cohort with WGS using PLINK 1.9 software (www.cog-genomics.org/plink/),[68] and further QC was performed as described.[60,69] Similarly, SNPs were extracted from the cross-sectional cohort with GWAS data and imputed on the basis of TOPMed reference panel using the Michigan Imputation Server.[70]

RNAseq data from BECs in the longitudinal cohort were extracted for 14 candidate genes (except for *ZPBP2* and *LRRC3C*, which failed QC) in the chr17q12-21.2 region. In brief, Illumina HiSeq RNAseq reads were quality filtered and mapped to human genome hg38 using STAR package.[71] Read counts were regularized logarithm transformed using the DESeq2 package.[72] The RNAseq data will be deposited and accessible through GEO (www.ncbi.nlm.nih.gov/geo/). Agilent Whole Human Genome Microarray expression data of these 16 genes were extracted from BECs in the cross-sectional cohort as described.[73,74] The microarray expression data have been deposited and can be accessed through GSE63142 and GSE43696.[73,75,76]

Genetic association analysis. Logistic or linear regression, assuming a genetic additive model, was used for genetic association analysis of asthma severity (426 severe asthma vs 531 nonsevere asthma) and the number of exacerbations (n = 273) due to asthma in 3 years in non-Hispanic white adults (age ≥ 12 years) in the longitudinal cohort (Table I), adjusted for age, sex, and the first 5 components from the multidimensional scaling analysis of genome.

We first investigated a set of 48 candidate SNPs identified by a previous GWAS of asthma, allergy, and AD (NHGRI-EBI GWAS catalog[77]; www.ebi.ac.uk/gwas/) incorporated in UCSC genome browser (genome.ucsc.edu; accessed on August 12, 2019)[78] for association with asthma severity and

TABLE I. Demographic characteristics (mean ± SD) of subjects in the SARP cohort

	RNAseq (BECs) longitudinal		Microarray (BECs) cross-sectional		WGS*				
Characteristic	**All**	**WGS**	**All**	**GWAS**	**Severe asthma**	**Nonsevere asthma**	**Longitudinal exacerbations**	**Non-Hispanic white**	**African American**
n	156	114	155	120	426	531	273	1,016	622
Age (y), mean ± SD	41 ± 13	41 ± 13	37 ± 13	36 ± 13	46 ± 15	37 ± 15	47 ± 16	39 ± 17	29 ± 17
Sex: female, n (%)	99 (63)	74 (65)	101 (65)	80 (67)	269 (63)	353 (66)	176 (64)	656 (65)	369 (59)
BMI, mean ± SD	30 ± 8.1	30 ± 8.7	30 ± 6.8	30 ± 7.0	31 ± 7.7	28 ± 7.6	31 ± 7.9	29 ± 7.9	30 ± 11
Race (non-Hispanic white/African American/other†), %	67/24/9	65/26/9	62/29/9	60/29/11	100/0/0	100/0/0	100/0/0	100/0/0	0/100/0
Baseline % predicted FEV_1, mean ± SD	82 ± 21	76 ± 20	76 ± 22	76 ± 23	66 ± 22	84 ± 17	73 ± 21	77 ± 21	78 ± 20
Baseline FEV_1/FVC, mean ± SD	0.73 ± 0.10	0.70 ± 0.10	0.72 ± 0.12	0.71 ± 0.13	0.66 ± 0.13	0.75 ± 0.09	0.69 ± 0.11	0.72 ± 0.12	0.72 ± 0.11
Asthma status (control/nonsevere/severe), n	42/49/65	0/49/65	27/78/50	19/60/41	0/0/426	0/531/0	0/111/162	0/564/451	0/270/252
Age onset of asthma < 18 y, n (%)	77 (68)	77 (68)	88 (71)	69 (68)	238 (56)	348 (66)	164 (60)	645 (64)	394 (75)

BMI, Body mass index; *FVC*, forced vital capacity; *Microarray*, agilent whole human genome microarray 4x44K v2.
*A total of 1016 non-Hispanic whites and 622 African Americans in SARP longitudinal and cross-sectional cohorts with WGS were used for LD calculation; Among 1016 non-Hispanic whites, 957 adults (age, ≥12 y) (426 with severe asthma vs 531 with nonsevere asthma) were included in the genetic association analysis of asthma severity; 273 adults in the longitudinal cohort were included in the genetic association analysis of longitudinal asthma exacerbations.
†Other races include Hispanic, Asian, American Indian, and mixed.

longitudinal exacerbations in SARP (Fig 1). To reduce multiple tests due to SNPs with strong LD, the numbers of independent tests were calculated using GEC.[79] A total of 14.4 independent tests of 48 candidate SNPs were indicated by GECs, and thus SNPs with *P* value less than .0035 (0.05/14.4 tests) were considered significant. SNPs with *P* value less than .05 were considered as nominally significant. From all sequenced SNPs in the chr17q12-21.2 region, we extracted 1266 common SNPs (minor allele frequency [MAF] ≥ 0.01) to test for association and *P* value less than .05 was considered as nominally significant due to relatively small sample size. Note that all the 48 candidate SNPs were included in the set of 1266 common SNPs. LD was estimated with 95% CIs of D' to define LD blocks, and LD plots of candidate SNPs in the chr17q12-21.2 region were generated separately for 1016 non-Hispanic whites and 622 African Americans (Table I) using Haploview.[80]

eQTL analysis. A linear additive genetic model was used to test the association between SNPs and inverse normalized expression data as described before.[73,74] The longitudinal and cross-sectional cohorts were used as discovery and replication data sets, respectively (Fig 1). Significant eQTL SNPs identified in the lung tissue (n = 383) from Genotype-Tissue Expression database[26] were also evidence for replication (Fig 1). In the longitudinal cohort with WGS and RNAseq in BECs (n = 114), 252.6 independent tests of 862 common SNPs (MAF ≥ 0.05) in the chr17q12-21.2 region were indicated by GECs,[79] and thus, SNPs with *P* value less than 1.98×10^{-4} (0.05/252.6 tests) were considered as significant eQTL SNPs. SNPs with *P* value less than .05 were considered as nominally significant. Conditional eQTL analysis of *PGAP3*, *GSDMB*, and *GSDMA* in the longitudinal cohort was performed to identify independent eQTL SNPs by stepwise adjusting the most significant eQTL SNP.

Colocalization analysis. To test whether the same SNP (n = 862) is responsible for the genetic association of asthma severity and eQTL of *PGAP3*, *GSDMB*, or *GSDMA* in the longitudinal cohort (Fig 1), a Bayesian-based colocalization analysis was performed using coloc package.[81] A posterior probability of 75% or greater was considered as strong evidence of colocalization. Colocalization analysis of SNPs associated with asthma severity or longitudinal asthma exacerbations and with gene expression of

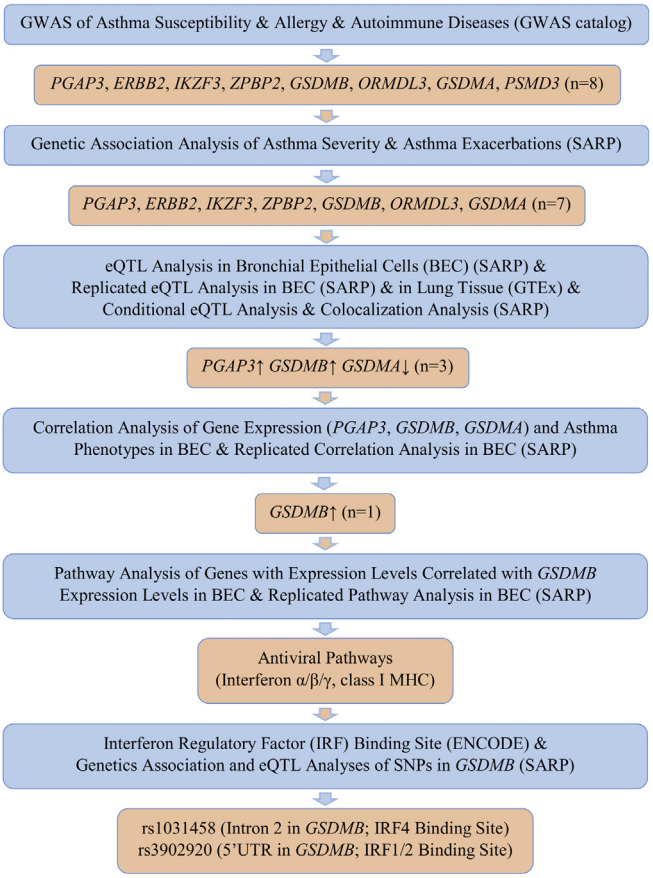

FIG 1. Flowchart of genetic analyses in the chr17q12-21.2 region.

PGAP3, *GSDMB*, or *GSDMA* in the longitudinal cohort (Fig 1) was also performed through conditional eQTL analysis by adjusting the most significant SNP associated with asthma severity or longitudinal asthma exacerbations.

Correlation analysis of gene expression and asthma phenotypes. Correlation analysis of gene expression and asthma-related phenotypes was performed as described (Fig 1).[73,74] In brief, a generalized linear model was used to test the correlation between expression levels of 16 candidate genes and asthma-related phenotypes with adjustment for age, sex, race (dummy variables for non-Hispanic whites and African Americans), body mass index, and batch effect. *P* value less than .05 was considered as nominally significant.

Pathway analysis. Correlation analysis of gene expression levels of 16,068 genes in the longitudinal cohort or 19,567 genes in the cross-sectional cohort was performed using Spearman rank correlation. The genes with expression levels significantly correlated with *PGAP3*, *GSDMB*, or *GSDMA* ($P < .05/16{,}067 = 3.1 \times 10^{-6}$ in the longitudinal cohort and $P < .05/19{,}566 = 2.5 \times 10^{-6}$ in the cross-sectional cohort) were input into Reactome software for pathway analysis[82] (Fig 1). Enriched biological pathways were identified using a hypergeometric distribution test with false-discovery rate–adjusted *P* value of less than .05.

IFN regulatory factor binding site analysis. IFN regulatory factor (IRF) binding sites were checked for *GSDMB* based on ENCODE database (Fig 1).[83] Genetic association and eQTL analyses were performed for 2 common SNPs and 4 rare SNPs (MAF < 0.01) in the identified IRF binding sites of *GSDMB*.

RESULTS

Genetic association analysis

Sixteen candidate genes in the chr17q12-21.2 region (see Fig E1 in this article's Online Repository at www.jacionline.org) were selected on the basis of published GWASs of asthma, allergy, or AD.[77] To elucidate shared genetic variants for immune diseases, 48 SNPs in this region identified through GWASs of asthma, allergy, and AD[77,78] or associated with asthma as reported by Stein et al[61] were investigated (Table II).

Most of the SNPs previously associated with asthma susceptibility were associated with asthma severity at the nominal *P* value of .05 (Table II). rs2305479 and rs62067034 in *GSDMB* were significantly associated with asthma severity after multiple-test adjustment (odds ratio, 1.34; $P = .0029 < .0035$). When testing 1266 common SNPs, several independent signals were associated with asthma severity though no SNP reached a more stringent significance ($P < .05/1266$) (see Table E2 in this article's Online Repository at www.jacionline.org), including 5 SNPs in *GSDMB* (odds ratio, >1.3; $P < .0035$) with the risk alleles associated with increased *GSDMB* expression.

Most of the SNPs previously associated with asthma susceptibility were also associated with longitudinal asthma exacerbations at the nominal *P* value of .05 (Table II). rs2517955 in *PGAP3* was significantly associated with longitudinal asthma exacerbations after multiple-test adjustment ($P = .0034$). When testing 1266 common SNPs, several independent signals were associated with longitudinal asthma exacerbations though no SNP reached stringent significance ($P < .05/1266$) (see Table E3 in this article's Online Repository at www.jacionline.org), including 4 SNPs in the *PGAP3-ERBB2* region ($P < .0035$) with the risk alleles associated with increased *PGAP3* expression.

Multiple SNPs in this region were associated with asthma, allergy, and AD; however, the risk alleles were opposite between asthma and AD (Table II). For example, the G allele of rs907092 in *IKZF3* was the risk allele for asthma ($P < 5 \times 10^{-8}$)[7,8] and asthma severity ($P = .027$), and associated with higher expression levels of *GSDMB* ($P = 3.7 \times 10^{-4}$) and *PGAP3* ($P = 7.9 \times 10^{-4}$), but was the protective allele for primary biliary cholangitis ($P < 5 \times 10^{-8}$).[38] The G allele of rs2305480 (a missense mutation in *GSDMB*) was the risk allele for asthma ($P < 5 \times 10^{-8}$),[14,15] asthma severity ($P = .015$), and longitudinal asthma exacerbations ($P = .0086$) and was associated with higher expression levels of *GSDMB* ($P = 2.5 \times 10^{-5}$), but was the protective allele for rheumatoid arthritis and ulcerative colitis ($P < 5 \times 10^{-8}$).[47,56] The A allele of rs3894194 (a missense mutation in *GSDMA*) was the risk allele for asthma ($P < 5 \times 10^{-8}$)[14,15] and was associated with lower expression levels of *GSDMA* ($P = 4.3 \times 10^{-4}$), but was the protective allele for systemic sclerosis ($P < 5 \times 10^{-8}$).[58] All 48 candidate SNPs identified by the previous GWAS (Table II) were common SNPs (MAF ≥ 0.01), and thus, belonged to 1266 common SNPs analyzed in this study. When ranking genetic association of asthma severity *P* values of 1266 SNPs, 35 (73%), 6 (13%), 3 (6%), and 4 (8%) of 48 candidate SNPs were distributed in the first to fourth quartile, respectively.

eQTL analysis and colocalization analysis

Expression of 14 genes (except *ZPBP2* and *LRRC3C*) in the longitudinal cohort (n = 114 BECs) and 16 genes in the cross-sectional cohort (n = 120 BECs) passed QC (Table I and Table E1). LD pruning ($r^2 \geq 0.8$) of 862 common SNPs (MAF ≥ 0.05) belonging to these 16 candidate genes generated 273 SNPs. The complete eQTL results of 862 SNPs are summarized in Table E4 in this article's Online Repository at www.jacionline.org.

Twenty-six of 273 SNPs were significantly associated with the gene expression levels of *PGAP3*, *GSDMB*, or *GSDMA*, but not associated with the other genes in the longitudinal cohort (Table III; see Tables E4 and E5 in this article's Online Repository at www.jacionline.org). The eQTL findings of 26 SNPs in the longitudinal cohort were generally replicated in BECs in the cross-sectional cohort at a nominal *P* value of .05 (see Table E6 in this article's Online Repository at www.jacionline.org). Considering stringent replication ($P < .05/26 = 1.9 \times 10^{-3}$), 16 of 26 SNPs in *PGAP3* or *GSDMB* were replicated in BECs in the cross-sectional cohort; 21 of 26 SNPs in *PGAP3*, *GSDMB*, or *GSDMA* were replicated in Genotype-Tissue Expression database lung tissue (Table III); altogether, 22 of 26 SNPs were replicated. Three and 6 LD blocks were formed for these 26 SNPs in non-Hispanic whites and African Americans, respectively (Table III; see Figs E2 and E3 in this article's Online Repository at www.jacionline.org). SNPs in *PPP1R1B*, *PGAP3*, and *ERBB2* were associated with *PGAP3* expression. SNPs in the *IKZF3* region were associated with the expression levels of *PGAP3*, *GSDMB*, or *GSDMA*. SNPs in *ZPBP2*, *GSDMB*, and *ORMDL3* were associated with *GSDMB* expression. SNPs in *GSDMA* were associated with *GSDMA* expression. Most of these 26 eQTL SNPs were associated with asthma severity or longitudinal asthma exacerbations at a nominal *P* value of .05 (see Table E7 in this article's Online Repository at www.jacionline.org).

Five and 6 LD blocks were identified for 48 GWAS-identified SNPs in non-Hispanic whites and African Americans, respectively (Table II; see Figs E4 and E5 in this article's Online Repository at www.jacionline.org). Significant eQTL SNPs (*P* <

TABLE II. Genetic association and eQTL results of 48 GWAS-identified SNPs associated with expression levels of *PGAP3*, *GSDMB*, or *GSDMA* in the longitudinal cohort

SNP	Position (hg38)	SNP type	Gene	Allele*	Associated trait	LD† (NHW)	LD† (AA)	Asthma severity‡			No. of exacerbations in 3 y§		eQTL of SARP3 in BECs (n = 114)			eQTL of GTEx database lung tissue (n = 383)
								Effect allele	OR	*P*	*β*	*P*	PGAP3 *β* (*P*)	GSDMB *β* (*P*)	GSDMA *β* (*P*)	
rs2941504‖	39674647	Synonymous	*PGAP3*	A/G	Asthma[2]; eQTL for PGAP3[3]	1	1	A	1.05	.64	0.97	.011	0.77 (5×10^{-9})	0.30 (.03)	−0.32 (.02)	A ~ PGAP3↑ (2×10^{-10}); ORMDL3↑ (1×10^{-7}); GSDMA↓ (4×10^{-6})
rs2517955‖	39687428	Intronic	*PGAP3*	C/T	eQTL for ORMDL3[4]			C	1.10	.35	**1.05**	**.0034**	0.56 (5×10^{-6})	0.28 (.03)	−0.11 (.4)	C ~ PGAP3↑ (1×10^{-12}); ORMDL3↑ (2×10^{-6})
rs2952156‖,¶	39720582	Intronic	*ERBB2*	A/G	Asthma[5]	2		A	1.06	.56	0.99	.0081	0.76 (4×10^{-8})	0.30 (.04)	−0.33 (.02)	A ~ PGAP3↑ (4×10^{-10}); ORMDL3↑ (4×10^{-9}); GSDMA↓ (7×10^{-6}); GSDMB↑ (2×10^{-5})
rs4252665¶	39729130	Intronic	*ERBB2*	T/C	SLE[31]			T	0.69	.15	−0.40	.69	−0.02 (1.0)	0.04 (.9)	−0.28 (.5)	NS
rs2941522¶	39754115	Intergenic	*GRB7-IKZF3*	T/C	Asthma[6]			T	1.24	.028	0.84	.019	0.45 (8×10^{-4})	0.33 (.02)	−0.54 (6×10^{-5})	T ~ GSDMB↑ (3×10^{-15}); ORMDL3↑ (4×10^{-15}); GSDMA↓ (1×10^{-6}); PGAP3↑ (1×10^{-6})
rs12946510¶	39756124	Intergenic	*GRB7-IKZF3*	T/C	UC[32,33]; CD[32,33]; MS[34]; IBD[32,33,35]		2	T	0.86	.12	−0.72	.046	−0.43 (.002)	−0.43 (.002)	0.44 (.002)	T ~ GSDMB↓ (2×10^{-9}); ORMDL3↓ (9×10^{-9}); GSDMA↑ (1×10^{-6})
rs2941509¶	39764941	3′ UTR	*IKZF3*	A/G	SLE[36,37]			A	0.81	.44	0.46	.65	−0.08 (.7)	0.04 (.9)	0.02 (.9)	A ~ GSDMB↓ (3×10^{-5})
rs907092‖,¶	39766006	Synonymous	*IKZF3*	G/A A/G	Asthma[7,8]; PBCh[38]			G	1.24	.027	0.66	.069	0.47 (8×10^{-4})	0.50 (4×10^{-4})	−0.43 (.003)	G ~ GSDMB↑ (2×10^{-9}); ORMDL3↑ (5×10^{-9}); GSDMA↓ (2×10^{-7})
rs10445308¶	39781794	Intronic	*IKZF3*	C/T	Atopy[27]			C	1.23	.033	0.76	.034	0.47 (7×10^{-4})	0.51 (2×10^{-4})	−0.45 (1×10^{-3})	C ~ GSDMB↑ (7×10^{-10}); ORMDL3↑ (3×10^{-9}); GSDMA↓ (3×10^{-8})
rs12450323¶	39816455	Intronic	*IKZF3*	T/G	Asthma[9]			T	1.15	.24	0.96	.023	0.63 (2×10^{-4})	0.43 (.01)	0.13 (.4)	T ~ ORMDL3↑ (1×10^{-5}); GSDMB↑ (2×10^{-5}); PGAP3↑ (2×10^{-5})
rs9303277‖,¶	39820216	Intronic	*IKZF3*	T/C	PBCh[39-42]; SS[43]; SLE[43]			T	0.79	.017	−0.84	.017	−0.48 (4×10^{-4})	−0.40 (.004)	0.49 (3×10^{-4})	T ~ GSDMB↓ (7×10^{-15}); ORMDL3↓ (6×10^{-14}); GSDMA↑ (2×10^{-7}); PGAP3↓ (7×10^{-6})
rs143123127¶	39850937	Intronic	*IKZF3*	A/G	SLE[37]			A	0.80	.43	−0.38	.73	−0.02 (1.0)	0.30 (.5)	−0.77 (.06)	NA
rs9635726¶	39863888	Intronic	*IKZF3*	C/T	PBCh[44]			C	0.88	.27	−1.14	.0078	−0.63 (1×10^{-4})	−0.47 (.005)	−0.07 (.7)	C ~ GSDMB↓ (1×10^{-5}); ORMDL3↓ (2×10^{-5}); PGAP3↓ (2×10^{-5})
rs4795397¶	39867492	Intergenic	*IKZF3-ZPBP2*	A/G (G/A)	Asthma[8] IBD[33]			A	1.17	.027	0.81	.022	0.40 (.003)	0.52 (1×10^{-4})	−0.42 (.002)	A ~ ORMDL3↑ (4×10^{-9}); GSDMA↓ (2×10^{-8}); GSDMB↑ (7×10^{-8})

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TABLE II. *(Continued)*

SNP	Position (hg38)	SNP type	Gene	Allele*	Associated trait	LD† (NHW)	LD† (AA)	Asthma severity‡			No. of exacerbations in 3 y§		eQTL of SARP3 in BECs (n = 114)			eQTL of GTEx database lung tissue (n = 383)
								Effect allele	OR	*P*	*β*	*P*	PGAP3 *β* (*P*)	GSDMB *β* (*P*)	GSDMA *β* (*P*)	
rs11655198¶	39869916	Intronic	*ZPBP2*	(C/T)	Asthma[10]		3	C	1.29	.0097	0.82	.019	0.40 (.003)	0.44 (.001)	−0.30 (.03)	C ~ GSDMB↑ (6×10^{-15}); ORMDL3↑ (8×10^{-12}); GSDMA↓ (8×10^{-7}); PGAP3↑ (3×10^{-6})
rs12936231‖	39872867	Intronic	*ZPBP2*	(C/G)	ORMDL3 promoter[11]			C	1.29	.0089	0.87	.013	0.40 (.004)	0.42 (.002)	−0.37 (.008)	C ~ GSDMB↑ (5×10^{-15}); ORMDL3↑ (1×10^{-14}); GSDMA↓ (1×10^{-7}); PGAP3↑ (8×10^{-6})
rs59716545¶	39875604	Intronic	*ZPBP2*	(G/T)	RA[28]			G	0.82	.042	−0.89	.012	−0.38 (.005)	−0.52 (1×10^{-4})	0.31 (.02)	NA
rs12939457¶	39875935	Intronic	*ZPBP2*	T/C	Allergic rhinitis[28]			T	1.21	.054	0.90	.011	0.44 (.002)	0.50 (3×10^{-4})	−0.40 (.004)	NA
rs35736272¶	39876427	Intronic	*ZPBP2*	(C/T)	AD[45]			C	0.81	.033	−0.89	.012	−0.40 (.003)	−0.53 (6×10^{-5})	0.35 (.01)	C ~ ORMDL3↓ (7×10^{-10}); GSDMB↓ (3×10^{-9}); GSDMA↑ (4×10^{-9});
rs12232497¶	39883866	Intergenic	*ZPBP2-GSDMB*	C/T	AD[46]			C	0.81	.033	−0.89	.012	−0.40 (.003)	−0.53 (6×10^{-5})	0.35 (.01)	C ~ ORMDL3↓ (7×10^{-10}); GSDMA↑ (3×10^{-9}); GSDMB↓ (3×10^{-9})
rs2872507¶	39884510	Intergenic	*ZPBP2-GSDMB*	A/G	RA[47,48]; T1D[49]; UC[50]; CD[51,52]			A	0.81	.035	−0.89	.012	−0.42 (.002)	−0.51 (2×10^{-4})	0.35 (.01)	A ~ ORMDL3↓ (3×10^{-10}); GSDMB↓ (5×10^{-10}); GSDMA↑ (2×10^{-9})
rs12936409¶	39887396	Intergenic	*ZPBP2-GSDMB*	T/C	RA[47,53]			T	0.81	.030	−0.88	.014	−0.43 (.002)	−0.52 (1×10^{-4})	0.36 (.009)	T ~ ORMDL3↓ (8×10^{-10}); GSDMA↑ (4×10^{-9}); GSDMB↓ (9×10^{-9})
rs8067378¶	39895095	Intergenic	*ZPBP2-GSDMB*	G/A	PBCi[54]			G	0.76	.0054	−0.88	.011	−0.43 (.002)	−0.42 (.003)	0.36 (.01)	G ~ GSDMB↓ (5×10^{-15}); ORMDL3↓ (1×10^{-14}); GSDMA↑ (1×10^{-7}); PGAP3↓ (8×10^{-6})
rs12453507¶	39896954	Intergenic	*ZPBP2-GSDMB*	(G/C)	T1D[55]			G	0.76	.0050	−0.78	.024	−0.36 (.007)	−0.43 (1×10^{-3})	0.29 (.03)	G ~ GSDMB↓ (2×10^{-15}); ORMDL3↓ (2×10^{-12}); GSDMA↑ (2×10^{-8}); PGAP3↓ (1×10^{-6})
rs8069176‖,¶	39900944	Intergenic	*ZPBP2-GSDMB*	G/A	Asthma[5]			G	1.26	.020	0.86	.015	0.39 (.003)	0.57 (9×10^{-6})	−0.33 (.01)	G ~ ORMDL3↑ (6×10^{-11}); GSDMA↓ (1×10^{-10}); GSDMB↑ (2×10^{-10})
rs4795399¶	39905186	Intronic	*GSDMB*	T/C	Asthma[12,13]			T	1.26	.019	0.88	.013	0.35 (.007)	0.55 (2×10^{-5})	−0.31 (.02)	T ~ ORMDL3↑ (1×10^{-10}); GSDMA↓ (2×10^{-10}); GSDMB↑ (7×10^{-10})

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TABLE II. *(Continued)*

SNP	Position (hg38)	SNP type	Gene	Allele*	Associated trait	LD† (NHW)	LD† (AA)	Asthma severity‡			No. of exacerbations in 3 y§		eQTL of SARP3 in BECs (n = 114)			eQTL of GTEx database lung tissue (n = 383)
								Effect allele	OR	*P*	*β*	*P*	PGAP3 *β* (*P*)	GSDMB *β* (*P*)	GSDMA *β* (*P*)	
rs2305480‖,¶	39905943	Missense	*GSDMB*	G/A A/G	Asthma[14,15] RA[47]; UC[56]			G	1.27	.015	0.93	.0086	0.35 (.007)	0.55 (3×10^{-5})	−0.31 (.02)	G ~ ORMDL3↑ (1×10^{-10}); GSDMA↓ (2×10^{-10}); GSDMB↑ (2×10^{-9})
rs2305479¶	39905964	Missense	*GSDMB*	(C/T)	Asthma[5]			C	**1.34**	**.0029**	0.85	.014	0.33 (.01)	0.46 (3×10^{-4})	−0.26 (.05)	C ~ GSDMB↑ (6×10^{-15}); ORMDL3↑ (4×10^{-15}); GSDMA↓ (1×10^{-7}); PGAP3↑ (5×10^{-6})
rs62067034¶	39907485	Intronic	*GSDMB*	(C/T)	Asthma[16]			C	**1.34**	**.0029**	0.85	.014	0.33 (.01)	0.46 (3×10^{-4})	−0.26 (.05)	C ~ GSDMB↑ (2×10^{-15}); ORMDL3↑ (1×10^{-12}); GSDMA↓ (1×10^{-7}); PGAP3↑ (7×10^{-6})
rs11078927‖,¶	39908152	Intronic	*GSDMB*	C/T	Asthma[8,17]			C	1.26	.018	0.95	.0073	0.37 (.005)	0.56 (2×10^{-5})	−0.35 (.009)	C ~ ORMDL3↑ (1×10^{-10}); GSDMA↓ (3×10^{-10}); GSDMB↑ (9×10^{-10})
rs11078928‖	39908216	Splice receptor	*GSDMB*	T/C	eQTL for GSDMB[18]			T	1.26	.018	0.95	.0073	0.37 (.005)	0.56 (2×10^{-5})	−0.35 (.009)	T ~ ORMDL3↑ (8×10^{-11}); GSDMA↓ (4×10^{-10}); GSDMB↑ (8×10^{-10})
rs117097909¶	39908718	Intronic	*GSDMB*	A/G	Asthma[13]			A	1.04	.860	−0.04	.95	0.27 (.37)	0.52 (.09)	0.21 (.49)	NA
rs2290400‖,¶	39909987	Intronic	*GSDMB*	T/C (C/T)	Asthma[19] T1D[57]	3	4	T	1.32	.0044	0.84	.016	0.40 (.003)	0.41 (.003)	−0.35 (.01)	T ~ GSDMB↑ (8×10^{-16}); ORMDL3↑ (7×10^{-15}); GSDMA↓ (1×10^{-8}); PGAP3↑ (3×10^{-6})
rs4795400¶	39910767	Intronic	*GSDMB*	(C/T)	Allergy[10]			C	1.27	.015	0.91	.0093	0.35 (.007)	0.55 (3×10^{-5})	−0.31 (.02)	C ~ ORMDL3↑ (2×10^{-10}); GSDMB↑ (3×10^{-10}); GSDMA↓ (5×10^{-10})
rs869402¶	39911790	Intronic	*GSDMB*	(C/T)	Asthma[20]			C	1.33	.0039	0.81	.019	0.31 (.01)	0.41 (1×10^{-3})	−0.24 (.06)	C ~ GSDMB↑ (1×10^{-15}); ORMDL3↑ (2×10^{-12}); GSDMA↓ (2×10^{-7}); PGAP3↑ (3×10^{-6})
rs921650¶	39912823	Intronic	*GSDMB*	A/G	Allergy[29]			A	1.32	.0045	0.80	.021	0.33 (.009)	0.47 (2×10^{-4})	−0.27 (.03)	A ~ GSDMB↑ (1×10^{-15}); ORMDL3↑ (8×10^{-13}); GSDMA↓ (2×10^{-7}); PGAP3↑ (3×10^{-6})
rs7216389‖,¶	39913696	Intronic	*GSDMB*	T/C	Asthma[1]			T	1.32	.0045	0.80	.021	0.33 (.009)	0.47 (2×10^{-4})	−0.27 (.03)	T ~ GSDMB↑ (1×10^{-15}); ORMDL3↑ (8×10^{-13}); GSDMA↓ (2×10^{-7}); PGAP3↑ (3×10^{-6})

(Continued)

TABLE II. *(Continued)*

SNP	Position (hg38)	SNP type	Gene	Allele*	Associated trait	LD† (NHW)	LD† (AA)	Asthma severity‡ Effect allele	OR	*P*	No. of exacerbations in 3 y§ *β*	*P*	eQTL of SARP3 in BECs (n = 114) PGAP3 *β* (*P*)	GSDMB *β* (*P*)	GSDMA *β* (*P*)	eQTL of GTEx database lung tissue (n = 383)
rs9303280¶	39917778	Intronic	*GSDMB*	C/T	Allergy[30]			C	1.32	.0049	0.77	.028	0.37 (.004)	0.49 (1×10^{-4})	−0.33 (.01)	C ~ GSDMB↑ (3×10^{-15}); ORMDL3↑ (2×10^{-12}); GSDMA↓ (3×10^{-9}); PGAP3↑ (9×10^{-6})
rs4065275‖	39924612	Intronic	*ORMDL3*	G/A	ORMDL3 promoter[11]			G	1.31	.0064	0.82	.020	0.31 (.02)	0.36 (.008)	−0.29 (.04)	G ~ GSDMB↑ (1×10^{-13}); ORMDL3↑ (1×10^{-13}); GSDMA↓ (6×10^{-11})
rs8076131‖	39924659	Intronic	*ORMDL3*	A/G	Early wheeze[21]			A	1.25	.022	0.85	.015	0.36 (.007)	0.47 (3×10^{-4})	−0.37 (.006)	A ~ GSDMA↓ (1×10^{-11}); ORMDL3↑ (7×10^{-11}); GSDMB↑ (1×10^{-9})
rs12603332‖	39926554	5′ UTR	*ORMDL3*	C/T	eQTL and meQTL for ORMDL3/ GSDMB[22,23]	4	5	C	1.31	.0060	0.83	.018	0.29 (.03)	0.40 (.003)	−0.44 (9×10^{-4})	C ~ ORMDL3↑ (2×10^{-14}); GSDMB↑ (2×10^{-13}); GSDMA↓ (6×10^{-12}); PGAP3↑ (2×10^{-5})
rs4794820¶	39933091	Intronic	*ORMDL3*	(G/A)	Asthma[24]			G	1.26	.021	0.94	.0077	0.28 (.04)	0.40 (.002)	−0.38 (.004)	G ~ GSDMA↓ (2×10^{-17}); ORMDL3↑ (2×10^{-11}); GSDMB↑ (2×10^{-8})
rs6503525¶	39938921	Intergenic	*ORMDL3-LRRC3C*	(C/G)	Asthma[25]	5		C	1.23	.038	0.57	.12	0.25 (.06)	0.076 (.6)	−0.37 (.005)	C ~ GSDMA↓ (6×10^{-21}); GSDMB↑ (9×10^{-8}); ORMDL3↑ (2×10^{-5})
rs3902025¶	39963001	5′ UTR	*GSDMA*	C/A	SS[58]		6	C	0.81	.033	−0.65	.072	−0.30 (.02)	−0.23 (.09)	0.48 (3×10^{-4})	C ~ GSDMA↑ (2×10^{-21}); ORMDL3↓ (9×10^{-7}); GSDMB↓ (1×10^{-5})
rs3894194‖,¶	39965740	Missense	*GSDMA*	A/G G/A	Asthma[14,15] SS[59]			A	1.14	.20	0.33	.35	0.36 (.006)	0.10 (.4)	−0.46 (4×10^{-4})	A ~ GSDMA↓ (1×10^{-21}); GSDMB↑ (4×10^{-9}); ORMDL3↑ (2×10^{-7})
rs7212938¶	39966427	Missense	*GSDMA*	G/T	Asthma[9]			G	1.14	.19	0.28	.44	0.27 (.04)	0.14 (.3)	−0.28 (.03)	G ~ GSDMA↓ (3×10^{-18}); GSDMB↑ (1×10^{-7}); ORMDL3↑ (5×10^{-5})
rs3859192‖	39972395	Intronic	*GSDMA*	T/C	eQTL for GSDMA[26]			T	0.96	.68	0.44	.23	0.41 (.002)	0.19 (.2)	−0.42 (.001)	T ~ GSDMA↓ (5×10^{-52})
rs11652139¶	39992780	Intronic	*PSMD3*	(A/G)	Allergy[29]			A	1.01	.90	0.47	.19	0.32 (.02)	0.29 (.03)	−0.17 (.2)	NA

AA, African American; *CD*, Crohn disease; *GTEx*, Genotype-Tissue Expression; *IBD*, inflammatory bowel disease; *MS*, multiple sclerosis; *NA*, nonavailable; *NHW*, non-Hispanic white; *NS*, nonsignificant; *OR*, odds ratio; *PBCh*, primary biliary cholangitis; *PBCi*, primary biliary cirrhosis; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SS*, systemic sclerosis; *T1D*, type I diabetes; *UC*, ulcerative colitis.

Entries with *P* value <.0035 for genetic association analysis of asthma severity or longitudinal asthma exacerbations are bolded.

*Risk allele/other allele: parentheses indicate that the risk allele was not reported in the original study but predicted on the basis of available data.

†LD was estimated with 95% CIs of D' to define LD blocks of 48 SNPs for 1016 NHWs and 622 AAs in SARP longitudinal cohort and cross-sectional cohorts with WGS using Haploview.[80]

‡OR and *P* were OR and *P* value for genetic association analysis of asthma severity (426 severe vs 531 nonsevere asthma) in NHWs in the SARP cohort.

§β and *P* were correlation coefficient and *P* value for genetic association analysis of the number of longitudinal exacerbations due to asthma in 3 years in the longitudinal cohort in 273 patients with asthma with longitudinal asthma exacerbations in NHWs in the SARP cohort.

‖A total of 17 SNPs associated with asthma and reported by Stein et al.[61]

¶SNPs associated with asthma, allergy, and ADs from NHGRI-EBI GWAS catalog (www.ebi.ac.uk/gwas/),[77] incorporated in UCSC genome browser (genome.ucsc.edu; accessed on March 1, 2019).[78]

TABLE III. eQTL results of 26 SNPs significantly associated with expression levels of *PGAP3*, *GSDMB*, or *GSDMA* in the longitudinal cohort

						SARP3 BECs (n = 114)						
						PGAP3		GSDMB		GSDMA		eQTL of GTEx database
SNP	Position (hg38)	Gene	LD* (NHW)	LD* (AA)	A1	β	P	β	P	B	P	lung tissue (n = 383)†
rs3751903	39627534	*PPP1R1B*	1	1	C	0.43	.002	**0.55**	**1.0×10^{-4}**	−0.10	.5	C ~ PGAP3↑ (1×10^{-7})
rs3794712	39635234	*PPP1R1B*			A	0.48	.007	**0.78**	**6.5×10^{-6}**	0.06	.7	NS
rs10558975	39675051	*PGAP3*			G	**-0.54**	**1.1×10^{-5}**	−0.32	.01	0.13	.3	G ~ PGAP3↓ (1×10^{-13}); ORMDL3↓ (2×10^{-5}); GSDMB↓ (6×10^{-5})
rs907088	39677314	*PGAP3*		2	G	**0.69**	**3.3×10^{-7}**	0.32	.02	−0.27	.06	G ~ PGAP3↑ (1×10^{-12}); ORMDL3↑ (8×10^{-8})
rs2517954	39687297	*PGAP3*			T	**0.77**	**3.1×10^{-9}**	0.25	.08	−0.29	.04	T ~ PGAP3↑ (9×10^{-10}); ORMDL3↑ (3×10^{-8})
rs2904765	39692422	*PGAP3-ERBB2*			T	**0.70**	**8.7×10^{-6}**	0.17	.3	−0.34	.04	NS
rs56328874	39694273	*PGAP3-ERBB2*			A	**-0.72**	**1.0×10^{-4}**	0.16	.4	0.26	.2	NS
rs2517951	39696844	*PGAP3-ERBB2*	2	3	T	**-0.58**	**1.6×10^{-6}**	−0.29	.02	0.13	.3	T ~ PGAP3↓ (1×10^{-13}); ORMDL3↓ (2×10^{-6}); GSDMB↓ (2×10^{-5})
rs2952155	39705465	*ERBB2*			T	**0.72**	**4.6×10^{-7}**	0.31	.04	−0.23	.1	T ~ PGAP3↑ (2×10^{-8}); ORMDL3↑ (1×10^{-6})
rs2934967	39714125	*ERBB2*			G	**0.79**	**9.9×10^{-9}**	0.25	.08	−0.29	.05	G ~ PGAP3↑ (5×10^{-11}); ORMDL3↑ (2×10^{-8}); GSDMB↑ (4×10^{-5}); GSDMA↓ (6×10^{-6})
rs2941520	39747477	*GRB-IKZF3*		4	T	**0.70**	**1.7×10^{-6}**	0.30	.05	0.01	.9	T ~ PGAP3↑ (2×10^{-10}); ORMDL3↑ (3×10^{-9}); GSDMB↑ (1×10^{-6})
rs2941519	39747478	*GRB-IKZF3*			G	−0.36	.01	−0.15	.3	**0.52**	**1.6×10^{-4}**	G ~ ORMDL3↓ (5×10^{-14}); GSDMB↓ (6×10^{-13}); PGAP3↓ (5×10^{-6}); GSDMA↑ (3×10^{-5})
rs9747973	39748854	*GRB-IKZF3*			C	−0.41	.003	−0.34	.01	**0.53**	**1.0×10^{-4}**	C ~ GSDMB↓ (2×10^{-15}); ORMDL3↓ (7×10^{-15}); GSDMA↑ (6×10^{-7}); PGAP3↓ (1×10^{-6})
rs12450323	39816455	*IKZF3*			T	**0.63**	**1.5×10^{-4}**	0.43	.01	0.13	.4	T ~ ORMDL3↑ (1×10^{-5}); GSDMB↑ (2×10^{-5}); PGAP3↑ (2×10^{-5})
rs114211283	39819840	*IKZF3*			A	**1.11**	**3.5×10^{-5}**	0.13	.6	0.12	.7	NS
rs62066988	39836028	*IKZF3*			T	−0.35	.02	**−0.56**	**1.4×10^{-4}**	0.31	.04	T ~ ORMDL3↓ (2×10^{-6}); GSDMB↓ (2×10^{-5}); GSDMA↑ (4×10^{-5})
rs9635726	39863888	*IKZF3*	3		T	**0.63**	**1.3×10^{-4}**	0.47	.005	0.07	.7	T ~ GSDMB↑ (1×10^{-5}); ORMDL3↑ (2×10^{-5}); PGAP3↑ (2×10^{-5})
rs4795397	39867492	*IKZF3-ZPBP2*		5	G	−0.40	.003	**−0.52**	**1.0×10^{-4}**	0.42	.002	G ~ ORMDL3↓ (4×10^{-9}); GSDMA↑ (2×10^{-8}); GSDMB↓ (7×10^{-8})
rs12150079	39869164	*ZPBP2*			A	−0.38	.01	**−0.59**	**5.7×10^{-5}**	0.32	.03	A ~ ORMDL3↓ (3×10^{-7}); GSDMB↓ (6×10^{-6}); GSDMA↑ (7×10^{-6})
rs11651596	39899863	*ZPBP2-GSDMB*		6	C	−0.36	.008	**−0.62**	**1.6×10^{-6}**	0.32	.02	C ~ ORMDL3↓ (2×10^{-10}); GSDMA↑ (3×10^{-10}); GSDMB↓ (2×10^{-9})
rs11657449	39901588	*ZPBP2-GSDMB*			C	−0.34	.02	**−0.69**	**7.5×10^{-7}**	0.32	.03	C ~ ORMDL3↓ (2×10^{-7}); GSDMA↑ (7×10^{-7}); GSDMB↓ (6×10^{-6})

(Continued)

TABLE III. *(Continued)*

SNP	Position (hg38)	Gene	LD* (NHW)	LD* (AA)	A1	SARP3 BECs (n = 114) PGAP3 β	PGAP3 P	GSDMB β	GSDMB P	GSDMA B	GSDMA P	eQTL of GTEx database lung tissue (n = 383)†
rs1011082	39912261	*GSDMB*			T	−0.33	.01	**−0.51**	**6.6×10^{-5}**	0.31	.02	T ~ GSDMB↓ (8×10^{-16}); ORMDL3↓ (6×10^{-13}); GSDMA↑ (1×10^{-7}); PGAP3↓ (4×10^{-7})
rs201413617	39917590	*GSDMB-ORMDL3*			G	−0.33	.01	**−0.48**	**1.6×10^{-4}**	0.27	.04	NS
rs4795405	39932164	*ORMDL3-LRRC3C*			T	−0.35	.01	**−0.51**	**1.6×10^{-4}**	0.45	.0009	T ~ GSDMA↑ (3×10^{-14}); ORMDL3↓ (1×10^{-10}); GSDMB↓ ($P = 6 \times 10^{-10}$)
rs9914973	39966455	*GSDMA*			C	−0.42	.002	−0.22	.1	**0.52**	**1.7×10^{-4}**	C ~ GSDMA↑ (9×10^{-17})
rs3859193	39969603	*GSDMA*			A	0.31	.02	0.13	.3	**−0.50**	**7.2×10^{-5}**	A ~ GSDMA↓ (9×10^{-30}); GSDMB↑ (5×10^{-7})

AA, African American; *GTEx*, Genotype-Tissue Expression; *NHW*, non-Hispanic white; *NS*, nonsignificant.
Entries with $P < 1.98 \times 10^{-4}$ are bolded. β and *P* were correlation coefficient and *P* value of eQTL analysis. ↑indicates upregulation of gene expression and ↓indicates downregulation of gene expression.
*LD was estimated with 95% CIs of D' to define LD blocks of 26 SNPs for 1016 NHWs and 622 AAs in SARP longitudinal and cross-sectional cohorts with WGS using Haploview.[80]
†eQTL of GTEx database: eQTL SNPs identified in the lung tissue (n = 383) from GTEx database.[26]

.0035) were associated with the expression levels of 3 genes (*PGAP3*, *GSDMB*, or *GSDMA*) in the longitudinal cohort and were generally replicated in the cross-sectional cohort at a nominal *P* value of .05 (Table II; see Table E8 in this article's Online Repository at www.jacionline.org). Genotype-Tissue Expression database lung tissue eQTL in this region identified 4 genes (*PGAP3*, *GSDMB*, *ORMDL3*, and *GSDMA*) (Tables II and III).

Conditional eQTL analysis was performed by stepwise adjusting the most significant eQTL SNP (see Table E9 in this article's Online Repository at www.jacionline.org), and indicated that 2 SNPs (rs2517954 in *PGAP3* and rs114211283 in *IKZF3*), 2 SNPs (rs11657449 in *ZPBP2-GSDMB* and rs3794712 in *PPP1R1B*), and 1 SNP (rs3859193 in *GSDMA*) were independent eQTL SNPs for *PGAP3*, *GSDMB*, and *GSDMA*, respectively.

Colocalization analysis[81] of the signals from genetic association of asthma severity and eQTL was performed, and indicated no significant colocalization SNP based on the criterion of posterior probability greater than 75% (see Table E10 in this article's Online Repository at www.jacionline.org). rs2517954 in *PGAP3*, rs11657449 in *ZPBP2-GSDMB*, and rs2941522 in *GRB7-IKZF3* were top colocalization SNPs for *PGAP3*, *GSDMB*, and *GSDMA*, respectively (see Table E11 in this article's Online Repository at www.jacionline.org). Colocalization analysis between SNPs associated with asthma severity or longitudinal asthma exacerbations and gene expression of *PGAP3*, *GSDMB*, and *GSDMA* was also performed through conditional eQTL analysis by adjusting the most significant SNP associated with asthma severity or longitudinal asthma exacerbations (see Table E12 in this article's Online Repository at www.jacionline.org; Table II). With adjustment of rs2952156 in *ERBB2*, rs2305479 in *GSDMB*, and rs3902025 in *GSDMA*, all eQTL SNPs for *PGAP3* (except for rs114211283 in *IKZF3*), for *GSDMB* (except for 2 SNPs in *PPP1R1B* and *ZPBP2-GSDMB*), and for *GSDMA* became nonsignificant. For example, the association between *GSDMB* expression and rs11657449 in *ZPBP2-GSDMB* or rs3794712 in *PPP1R1B* was weakened when adjusting for rs2305479, indicating that rs2305479 partly accounted for the eQTL association but not completely. In summary, the colocalization analyses did not show strong evidence for colocalization.

Expression analysis and pathway analysis

The risk alleles associated with asthma, asthma severity, and longitudinal asthma exacerbations were associated with higher expression levels of *PGAP3* and *GSDMB* or the lower expression levels of *GSDMA* (Table II), which indicated that expression levels of *PGAP3*, *GSDMB*, and *GSDMA* may be correlated with asthma phenotypes.

Correlation analysis of gene expression (*PGAP3*, *GSDMB*, and *GSDMA*) and asthma phenotypes was performed in BECs in the longitudinal cohort (n = 156) and replicated in BECs (n = 155) in the cross-sectional cohort (Table IV). Higher expression levels of *GSDMB* were correlated with asthma ($P = .05$), greater number of exacerbations in the last 12 months ($P = .02$), and higher reduction in asthma control questionnaire-6 score after steroid treatment ($P = .0008$) in the longitudinal cohort. Higher expression levels of *GSDMB* were correlated with emergency room visits or hospitalizations due to asthma in the last 12 months ($P = .03$) in the cross-sectional cohort. Other asthma-related phenotypes were not correlated with expression levels of *PGAP3*, *GSDMB*, or *GSDMA* (see Table E13 in this article's Online Repository at www.jacionline.org), except that higher expression levels of *GSDMB* were correlated with higher fractional exhaled nitric oxide ($P = .03$) in the longitudinal cohort. Although correlation analysis was focused on *PGAP3*, *GSDMB*, and *GSDMA*, the other 13 genes were also analyzed (see Tables E14 and E15 in this article's Online Repository at www.jacionline.org). Higher expression of *PNMT* and lower expression of *CSF3* were associated with asthma susceptibility in BECs in the longitudinal and cross-sectional cohorts.

Pathway analyses were performed on the genes with expression levels significantly correlated with *PGAP3*, *GSDMB*, or *GSDMA*. No biological pathways were identified for the genes correlated with *PGAP3* or *GSDMA* after false-discovery rate adjustment (data not shown). A total of 435 and 677 genes were positively

TABLE IV. Correlation of the expression levels of *PGAP3, GSDMB,* or *GSDMA* and asthma phenotypes in the SARP cohort

RNAseq (156 BECs) in the longitudinal cohort										
	Asthma susceptibility			Asthma severity			No. of exacerbations (last 12 mo)		ΔACQ6 (after − before steroid treatment)	
Gene	Healthy controls (n = 42)	Asthma (n = 114)	*P* value	Nonsevere asthma (n = 49)	Severe asthma (n = 65)	*P* value	Correlation coefficient (β)	*P* value (n = 114)	Correlation coefficient (β)	*P* value (n = 109)
PGAP3	8.81 ± 0.22	8.88 ± 0.20	.08	8.90 ± 0.21	8.87 ± 0.20	.33	−0.84	.57	−0.12	.77
GSDMB	9.94 ± 0.25	10.1 ± 0.32	.05	10.1 ± 0.28	10.1 ± 0.35	.89	2.11	.019	−0.81	.0008
GSDMA	0.50 ± 0.15	0.55 ± 0.22	.26	0.52 ± 0.19	0.57 ± 0.24	.29	−1.40	.27	0.14	.69

Microarray (155 BECs) in the cross-sectional cohort									
	Asthma susceptibility			Asthma severity			Emergency room or hospitalization (last 12 mo)		
Gene	Healthy controls (n = 27)	Asthma (n = 128)	*P* value	Nonsevere asthma (n = 78)	Severe asthma (n = 50)	*P* value	No (n = 77)	Yes (n = 47)	*P* value
PGAP3	10.8 ± 0.22	10.8 ± 0.33	.43	10.8 ± 0.34	10.8 ± 0.31	.63	10.8 ± 0.35	10.8 ± 0.29	.57
GSDMB	10.5 ± 0.42	10.4 ± 0.47	.15	10.4 ± 0.45	10.4 ± 0.51	.23	10.3 ± 0.46	10.5 ± 0.49	.03
GSDMA	6.26 ± 0.15	6.21 ± 0.13	.02	6.21 ± 0.14	6.21 ± 0.12	.56	6.21 ± 0.13	6.20 ± 0.13	.41

A general linear model was used to test the correlation between gene expression levels (natural logarithm transformed in the longitudinal cohort or log2 transformed in the cross-sectional cohort) and asthma phenotypes with adjustment of age, sex, race, body mass index, and batch effect.

and negatively correlated with *GSDMB* ($P < 3.1 \times 10^{-6}$) in BECs in the longitudinal cohort, among which 636 genes were replicated in BECs in the cross-sectional cohort ($P < .05$) (see Table E16 in this article's Online Repository at www.jacionline.org). Pathway analysis[82] was performed on 1112 and 462 genes with expression levels significantly correlated with *GSDMB* expression in BECs in the longitudinal cohort ($P < 3.1 \times 10^{-6}$) and cross-sectional cohort ($P < 2.5 \times 10^{-6}$), respectively. Expression levels of *GSDMB* were correlated with genes involved in IFN-α/IFN-β/IFN-γ signaling, MHC class I antigen presentation, and immune system pathways (false-discovery rate–adjusted $P <$ .05) (Table V; see Table E17 in this article's Online Repository at www.jacionline.org).

IRF binding site analysis

IRF binding sites were checked for *GSDMB*, and 2 regions were identified on the basis of ENCODE database (see Fig E6 in this article's Online Repository at www.jacionline.org).[83] One IRF1/2 biding site was located at 5′UTR-exon 1-intron 1 region of *GSDMB* (see Fig E7 in this article's Online Repository at www.jacionline.org), and 1 IRF4 biding site was located at intron 2 of *GSDMB* (see Fig E8 in this article's Online Repository at www.jacionline.org). Two common SNPs and 4 rare SNPs were found in these 2 IRF biding sites based on SARP WGS (Table VI). Two common SNPs (rs1031458 and rs3902920) were associated with *GSDMB* expression, asthma severity, and longitudinal asthma exacerbations ($P < .05$), making them potential functional SNPs.

Risk alleles for asthma severity and longitudinal asthma exacerbations (Table VI) were the T allele of rs1031458 or the C allele of rs3902920, and they were also associated with early onset of asthma ($P < .005$) (see Table E18 in this article's Online Repository at www.jacionline.org), especially atopic early-onset asthma (age onset of asthma < 6 years) ($P < .00001$) (see Table E19 in this article's Online Repository at www.jacionline.org; Fig 2). Similarly, most of the top 10 SNPs associated with asthma severity (including rs3902920; Table E2) were also associated with asthma severity in the subjects with early-onset asthma (onset < 6 years) (see Table E20 in this article's Online Repository at www.jacionline.org). rs1031458 and rs3902920 were in strong LD ($r^2 \geq 0.8$) with multiple neighboring SNPs (Tables II and III) in non-Hispanic whites (see Table E21 in this article's Online Repository at www.jacionline.org). In African Americans, rs1031458 and rs3902920 were in strong LD with 3 (rs921650, rs7216389, and rs201413617) and 0 neighboring SNPs, respectively.

In summary, by using a unique set of gene expression data from lung cells of patients with asthma obtained using investigative bronchoscopy and by performing comprehensive genetic association, expression correlation, eQTL, and pathway analyses, we have narrowed down the chr17q12-21.2 region (16 candidate genes; 390 kbp) to 2 SNPs in *GSDMB* associated with asthma severity and asthma exacerbations potentially through antiviral pathways (Fig 1).

DISCUSSION

Almost all the SNPs identified by previous GWASs in *GSDMB* have now been shown to be associated with asthma severity and longitudinal asthma exacerbations, indicating that SNPs in *GSDMB* are associated with asthma susceptibility, asthma severity, and asthma exacerbations. Asthma and AD share extensive immunologic pathways; however, the risk alleles of the same associated SNPs in this region are consistently opposite for asthma and AD, which may indicate distinct immunopathogenesis processes. In addition to SNPs with MAF greater than or equal to 0.01, we investigated rare SNPs (MAF < 0.01; n = 4006) for association with asthma severity. Fourteen rare SNPs were associated with asthma severity at a nominal *P* value of .05 with large effect size (2.9 < odds ratio < 12) (see Table E22 in this article's Online Repository at www.jacionline.org). Replication of these rare SNPs is needed in larger cohorts with sequence data and asthma phenotypes. In conclusion, findings from genetic association of asthma susceptibility, asthma severity, and asthma exacerbations in this region are generally consistent; however, genetic association analysis cannot narrow down the 16 candidate genes because of strong and complicated LD structure in this region.

TABLE V. Biological pathways enriched for genes with expression levels correlated with *GSDMB* expression in BECs in the longitudinal cohort

Pathway	Gene	*P* value (FDR)
IFN-γ signaling	CIITA, HLA-A, HLA-B, HLA-C, HLA-F, IFNG, IFNGR2, IL20RA, IRF9, MID1, OAS2, OAS3, PML, SP110, SP140L, STAT1, SUMO1, TRIM14, TRIM22, TRIM25, TRIM26, TRIM38	2.3×10^{-14}
IFN-α/β signaling	BST2, HLA-A, HLA-B, HLA-C, HLA-F, IFI27, IRF9, MX2, OAS2, OAS3, STAT1, STAT2, USP18, XAF1	2.3×10^{-14}
Antigen presentation (folding, assembly, and peptide loading of class I MHC)	HLA-A, HLA-B, HLA-C, HLA-F, SEC24B, TAP1, TAP2, TAPBP	2.3×10^{-14}
ER-Phagosome pathway	HLA-A, HLA-B, HLA-C, HLA-F, IKBKB, PSMB9, PSMD8, PSME2, RAPSN, TAP1, TAP2, TAPBP	2.3×10^{-14}
IFN signaling	BST2, CIITA, HLA-F, IFI27, IFNG, IFNGR2, IL20RA, IRF9, MAPK1, MID1, MX2, NUP210, OAS2, OAS3, PML, SP110, SP140L, STAT1, STAT2, SUMO1, TRIM14, TRIM22, TRIM25, TRIM26, TRIM38, UBA7, USP18, XAF1	2.3×10^{-14}
Endosomal/vacuolar pathway	HLA-A, HLA-B, HLA-C, HLA-F	2.3×10^{-14}
Antigen processing-cross-presentation	HLA-A, HLA-B, HLA-C, HLA-F, IKBKB, ITGB5, PSMB9, PSMD8, PSME2, RAPSN, TAP1, TAP2, TAPBP	2.3×10^{-14}
Class I MHC-mediated antigen processing and presentation	ASB14, ASB4, ASB8, FBXL3, FBXO2, FBXO21, FBXO41, HLA-A, HLA-B, HLA-C, HLA-F, IKBKB, ITGB5, NARF, PJA2, POLL, PSMB9, PSMD8, PSME2, RAPSN, RBX1, RNF213, SEC24B, SIAH1, SKP1, TAP1, TAP2, TAPBP, TRIM36, TRIM39, UBA7, UBE2D2, UBE2D4, UBE2E3	3.5×10^{-13}
Immunoregulatory interactions (between a lymphoid and a nonlymphoid cell)	CD226, CLEC2D, HLA-A, HLA-B, HLA-C, HLA-F, RAET1E	6.3×10^{-11}
Cytokine signaling in immune system	ATF1, ATF2, CALM2, CIITA, CRKL, DUSP16, FASLG, HLA-A, HLA-B, HLA-C, HLA-F, IFI27, IKBKB, IL18BP, IL20RA, IL37, IL6ST, IRF9, LAMTOR3, LGALS9, LIFR, MID1, MX2, NDN, PDGFA, PML, PSME2, PTPN14, PTPN4, RBX1, SKP1, SP110, STAT1, STAT2, STAT6, TRIM14, TRIM22, TRIM25, TRIM26, TRIM38	7.9×10^{-08}
Adaptive immune system	ACTR10, ASB4, ASB8, ASB14, BLNK, BTF3, BTN2A1, BTN2A2, BTN3A1, CALM2, CARD11, CD74, CLEC2D, DCTN3, DCTN6, FBXL3, FBXO41, GRAP2, HLA-A, HLA-B, HLA-C, IKBKB, MAP3K14, POLL, PSMD8, RAET1E, SEC24B, SIAH1, SKP1, TAP1, TAP2, TBCB, TEP1, TRIM36, TRIM39, UBA7, UBE2D2, UBE2D4, UBE2E3, ZAP70	9.7×10^{-03}

ER, Endoplasmic reticulum; *FDR*, false-discovery rate.
Pathways with FDR-adjusted *P* value of <.05 were included.

TABLE VI. Genetic association and eQTL results of 6 SNPs in IRF binding site of *GSDMB* in the SARP cohort

SNP	Position (hg38)	SNP type	IRF binding sites	Allele*(MAF)	Asthma severity†	No. of exacerbations in 3 y‡	eQTL in BECs (n = 114) longitudinal cohort§			eQTL GTEx database lung tissue (n = 383)‖
					OR (*P*)	*β* (*P*)	PGAP3 *β* (*P*)	GSDMB *β* (*P*)	GSDMA *β* (*P*)	
rs1031458	39915920	Intronic	IRF4	G/T (0.45)	0.76 (.0053)	−0.77 (.028)	−0.36 (5.1×10^{-3})	−0.47 (2.4×10^{-4})	0.31 (.018)	GSDMB↓ (1×10^{-20}) ORMDL3↓ (3×10^{-19}) GSDMA↑ (1×10^{-14}) PGAP3↓ (1×10^{-7})
rs3902920	39918763	5′UTR	IRF1/2	T/C (0.46)	0.75 (.0027)	−0.88 (.012)	−0.29 (.036)	−0.45 (.0011)	0.27 (.047)	NA
rs77929191	39915767	Intronic	IRF4	A/G (0.0021)	0.37 (.40)	−2.9 (.47)	−0.44 (.54)	−1.26 (.078)	−0.045 (.95)	NS
rs536439445	39918670	5′UTR	IRF1/2	A/G (0.0052)	0.57 (.41)	−1.8 (.53)	0.77 (.45)	−1.40 (.17)	0.011 (.99)	NS
rs549170154	39918764	5′UTR	IRF1/2	C/T (0.0021)	0.68 (.74)	5.1 (.21)	0.20 (.78)	−0.18 (.80)	−0.012 (.99)	NA
rs540139228	39918797	5′UTR	IRF1/2	G/A (0.0010)	1.3 (.86)	−2.6 (.52)	NA	NA	NA	NA

GTEx, Genotype-Tissue Expression; *NA*, nonavailable; *NS*, nonsignificant; *OR*, odds ratio; *UTR*, untranslated region.
↑indicates upregulation of gene expression and ↓indicates downregulation of gene expression.
*Minor allele (effect allele)/major allele (MAF).
†OR and *P* were OR and *P* value for genetic association analysis of asthma severity (426 severe vs 531 nonsevere asthma) in non-Hispanic whites in the SARP cohort.
‡*β* and *P* were correlation coefficient and *P* value for genetic association analysis of the number of longitudinal exacerbations due to asthma in 3 y in the longitudinal cohort in 273 patints with asthma with longitudinal asthma exacerbations in non-Hispanic whites in the SARP cohort.
§*β* and *P* were correlation coefficient and *P* value for eQTL analysis in 114 subjects with RNAseq of BECs in the SARP longitudinal cohort.
‖eQTL of GTEx database: eQTL SNPs identified in the lung tissue (n = 383) from GTEx database.[26]

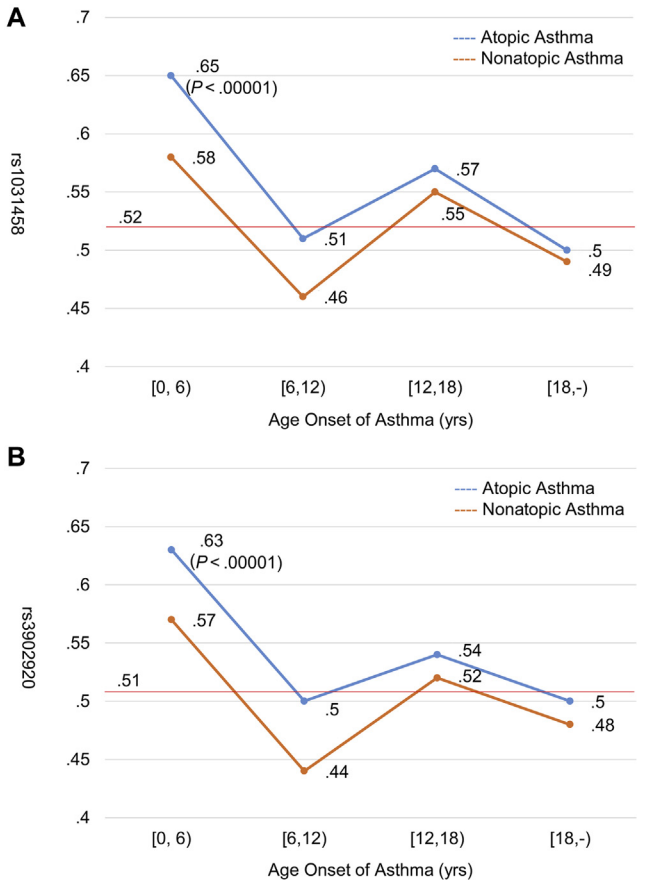

FIG 2. Risk allele frequency of (**A**) rs1031458 and (**B**) rs3902920 in *GSDMB* stratified by age onset of asthma and atopic status. Chi-square test was performed by comparing each asthma group with general North-Western European controls shown in red line (gnomAD V2.1.1; https://gnomad.broadinstitute.org/).

Gene expression is dependent on cell type or tissue, time, and environmental factors such as disease status. It is critical that cells are obtained from the appropriate organ (lung for asthma) and from living subjects with the disease being investigated instead of from surgical specimens (usually from cancer patients) or autopsy specimens. Even findings of eQTL analyses in lung cells are not always consistent (see Table E23 in this article's Online Repository at www.jacionline.org). The most significant eQTL genes were *GSDMA* followed by *GSDMB* and *ORMDL3* in 2 eQTL studies in lung tissue.[26,84] Nicodemus-Johnson et al[4] identified *ORMDL3* but not *GSDMB* in an eQTL analysis in BECs. Our eQTL analysis in BECs in both longitudinal and cross-sectional cohorts[73] identified *GSDMB* but not *ORMDL3*. Similarly, a recent genetic association and eQTL study has shown that eQTL SNPs for *GSDMB* (but not *ORMDL3*) in BECs play a major role in childhood asthma in African Americans.[85] BECs obtained from brush biopsies are mainly composed of epithelial cells, although a small proportion of basal cells and immune cells also exists. A flow cytometry study showed that 95% to 97% of the cells from bronchial brushings were epithelial cells.[86] In this study, cell populations were not available for every subject, and thus, were not adjusted. Future eQTL and expression analyses by adjusting cell composition or single-cell RNAseq may reveal interesting results.

SNPs in the *PGAP3-ERBB2* region were associated with *PGAP3* expression and longitudinal asthma exacerbations. In a previous GWAS, rs2941504 in *PGAP3* has been associated with asthma.[2] Another GWAS has identified rs2952156 in *ERBB2* associated with asthma[5] and *PGAP3* expression in lung tissue.[26] Thus, SNPs in *PGAP3-ERBB2* are associated with asthma phenotypes by upregulating *PGAP3* gene expression. The first GWAS of asthma has identified rs7216389 in *GSDMB* associated with childhood asthma and the expression levels of *ORMDL3* and *GSDMB* in lymphoblastoid cell lines.[1] In this study, rs7216389 was significantly associated with *GSDMB* expression ($P = 1.7 \times 10^{-4}$) but not *ORMDL3* ($P = .22$) in BECs. Thus, SNPs in *ZPBP2-GSDMB-ORMDL3* are associated with asthma phenotypes by upregulating *GSDMB* gene expression. rs3894194 in *GSDMA* has been associated with asthma[14,15] and the expression levels of *GSDMA* in lung tissue.[26] In this study, rs3894194 was significantly associated with *GSDMA* expression ($P = 4.3 \times 10^{-4}$). Thus, SNPs in *GSDMA* are associated with asthma phenotypes by downregulating *GSDMA* gene expression. Interestingly, SNPs in *IKZF3* were not consistently associated with a specific gene expression; instead, these were associated with the expression levels of *PGAP3*, *GSDMB*, or *GSDMA*, which may indicate long-distance gene expression regulation. Interaction between gene regulatory elements and genes shown by GeneHancer[87] also indicated that *IKZF3* was involved in complicated long-distance regulation of *GSDMB*, *GSDMA*, *ORMDL3*, and *ERBB2* (see Fig E9 in this article's Online Repository at www.jacionline.org). In summary, our findings confirm the hypothesis that there are proximal, core, and distal regions independently associated with asthma.[61] In addition, *IKZF3* forms a long-distance regulation region. More importantly, we narrowed down 16 candidate genes to 3 genes (*PGAP3*, *GSDMB*, and *GSDMA*).

We attempted to identify functional SNPs using colocalization and conditional eQTL analyses. rs2517954 for *PGAP3* and rs11657449 for *GSDMB* were identified by both colocalization analysis and conditional eQTL analysis, though the posterior probability of colocalization was not high. The probable reason is that the signals of genetic association are not strong due to sample size, and thus, eQTL signals drive the colocalization findings in SARP. Colocalization analysis through conditional eQTL analysis (Table E12) further indicates that the colocalization analysis based on the Bayesian approach does not show strong evidence for colocalization.

Previous studies have shown inconsistent relationship between gene expression in this region and asthma susceptibility.[61] The mRNA levels of *ORMDL3* in lymphoblastoid cell lines have not been significantly different in children with or without asthma.[1] An immunohistochemistry study has found that GSDMB protein levels are significantly higher in subjects with asthma than in controls.[88] In this study, higher mRNA levels of *GSDMB* were correlated with asthma and asthma exacerbations, though the correlation was not strong and not always consistently significant. Although our findings are based on relevant tissues (BECs) in relevant subjects (healthy controls, subjects with nonsevere asthma, and subjects with severe asthma), subjects involved in this study are all adults (age, ≥12 years). Typical of adult asthma cohorts, the SARP cohort consists of those with early onset of asthma and those with older age onset.[62,66] Because asthma is often an early-onset disease, expression or eQTL analyses in

children would be interesting, but, of course, research bronchoscopies are not performed in children. In this study, gene expression correlation and eQTL analyses were performed in all SARP subjects with mixed races to increase sample size and power. Although gene expression is less influenced by population stratification than genetic association, the findings may still be biased because of different allele frequencies and LD structures in different ethnic groups. Correlation analysis of gene expression (*PGAP3*, *GSDMB*, and *GSDMA*) and asthma phenotypes (Table IV) and eQTL analysis of top 5 eQTL SNPs for these 3 genes (Table E4) were also performed in SARP non-Hispanic whites (see Tables E24 and E25 in this article's Online Repository at www.jacionline.org). The findings of gene expression correlation and eQTL analyses were similar between non-Hispanic whites and all subjects with mixed races. In summary, the association of SNPs in *GSDMB*, the expression levels of *GSDMB*, and asthma phenotypes make *GSDMB* a strong candidate for severe asthma.

The function of *PGAP3*, *GSDMB*, or *GSDMA* is not totally understood. *PGAP3* may have a role in controlling autoimmunity and T_H1/T_H2 balance.[89] *GSDMA* may regulate or be regulated by TGF-β1 and mediate immune defense by inducing pyroptosis.[90] *GSDMB* may regulate apoptosis of epithelial cells and upregulate expression of airway remodeling genes, chemokines, and heat-shock proteins.[88,90] In this study, the expression levels of *GSDMB* are positively correlated with MHC class I molecules (*HLA-A/-B/-C/-F*), type I IFN (*STAT1*, *STAT2*, and *IRF9*) and type II IFN pathway genes (*IFN-γ* and *STAT1*), and T_H1 pathway genes (*IFN-γ*, *STAT1*, *IL18R1*, and *IL18BP*). All these biological pathways are related to the antiviral process, indicating that virus infection and expression of antiviral pathway genes may lead to severe asthma and asthma exacerbations. rs7216389 in *GSDMB* has been associated with human rhinovirus–induced wheezing illnesses in children and increased expression of *GSDMB* and *ORMDL3* in human rhinovirus–stimulated PBMCs, which further indicates the potential interaction of *GSDMB* and virus infection in asthma pathogenesis.[91] In a previous gene expression analysis in human nasal epithelial cells, *GSDMB* expression can be induced by IFN-α stimulation.[92] In this study, 2 SNPs (rs1031458 and rs3902920) in the promoter region of *GSDMB* are colocalized with IRF binding sites and associated with *GSDMB* expression, atopic early-onset asthma, asthma severity, and longitudinal asthma exacerbations, making them potential functional SNPs.

One main disadvantage of this study is the relatively small sample size. In genetic association, eQTL, and gene expression correlation analyses, nominal *P* values of .05 in addition to adjusted *P* values have been used. Furthermore, the replication results in several data sets are not always consistently significant. Thus, it requires careful interpretation as for significance and replication. One main advantage of this study is that multilevel evidence points to the same gene (*GSDMB*).

Conclusions

We identified that 3 independent signals (*PGAP3*, *GSDMB*, and *GSDMA*) were associated with asthma susceptibility, and *GSDMB* was also associated with asthma severity, asthma exacerbations, and antiviral pathways. Future candidate gene studies in large, multiethnic, or children with asthma and functional experiments may further reveal functional SNPs/genes for asthma including rare variants in this important region.

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Key messages

- **SNPs in *GSDMB* were associated with asthma, asthma severity, asthma exacerbations, and *GSDMB* expression levels, and its expression levels were correlated with asthma, asthma exacerbations, and antiviral pathways.**
- **SNPs in *PGAP3-ERBB2*, *ZPBP2-GSDMB-ORMDL3*, and *GSDMA* regions were associated with the expression levels of *PGAP3*, *GSDMB*, and *GSDMA*, respectively; SNPs in *IKZF3* were associated with the expression levels of *PGAP3*, *GSDMB*, or *GSDMA*.**
- **SNPs identified by GWASs of asthma or ADs were also eQTL SNPs for *PGAP3*, *GSDMB*, or *GSDMA*, but showed opposite effect alleles between asthma and AD.**

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