

Letters to the Editor

Large-scale, multiethnic genome-wide association study identifies novel loci contributing to asthma susceptibility in adults

To the Editor:

Asthma is a genetically heterogeneous disease. Although many recent genome-wide association studies (GWASs) have implicated multiple loci associated with asthma risk,¹⁻⁴ the impact of genetic variation on asthma susceptibility in large, ethnically diverse human populations has not been fully ascertained. Identifying the genetic variants associated with asthma in well-powered GWASs is crucial for discerning the genetic basis of asthma. Furthermore, it is also necessary to understand how genetic heterogeneity underlying asthma risk may be influenced by ethnic background. The objective of this study was to conduct a large-scale, transethnic GWAS of asthma in individuals in the Kaiser Permanente Northern California Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort.^{5,6}

Demographic information for GERA (68,623 asthma cases and nonasthmatic controls) is provided in Table E1 in this article's Online Repository at www.jacionline.org. GWASs were conducted for 4 racial/ethnic groups within GERA (non-Hispanic white, African American, Asian, and Hispanic), and replicated using

data from 2 large consortia, EVE and GABRIEL. Selected single nucleotide polymorphism (SNP) associations with potential functional consequences were profiled using bioinformatic methods. All study procedures were approved by the Institutional Review Board of the Kaiser Foundation Research Institute and Brigham and Women's Hospital. A detailed Methods section is provided in this article's Online Repository at www.jacionline.org.

In non-Hispanic whites, more than 7 million SNPs passed quality control measures and were evaluated by GWASs, of which 646 SNPs met genome-wide significance ($P < 5 \times 10^{-08}$) and were annotated to 2 regions of chromosomes 2 and 6 that include *IL1RL1/IL18R1* and *HLA-DQA1/HLA-DQB1*, respectively; of these, 5 SNPs were also genotyped in GABRIEL and 4 were suggestive in GABRIEL ($P < 1 \times 10^{-05}$) (Fig 1, A; Table I). Eighteen of the genome-wide significant GERA SNPs were also genotyped in EVE; of these, 14 were nominally significant ($P < .05$), and the top 2 SNPs were suggestive ($P < 1 \times 10^{-05}$) (Table I). Thus, a total of 16 GERA SNPs replicated in either EVE or GABRIEL, of which all were annotated to *HLA-DQA1* or *IL1RL1/IL18R1* loci (Fig 1, A; Table I). A survey of 32 published asthma GWASs cited in the National Human Genome Research Institute (NHGRI) Catalog revealed 113 suggestive associations ($P < 1 \times 10^{-05}$) (see Table E2 in this article's Online Repository at www.jacionline.org). Of these, 87 SNPs (77%) were also

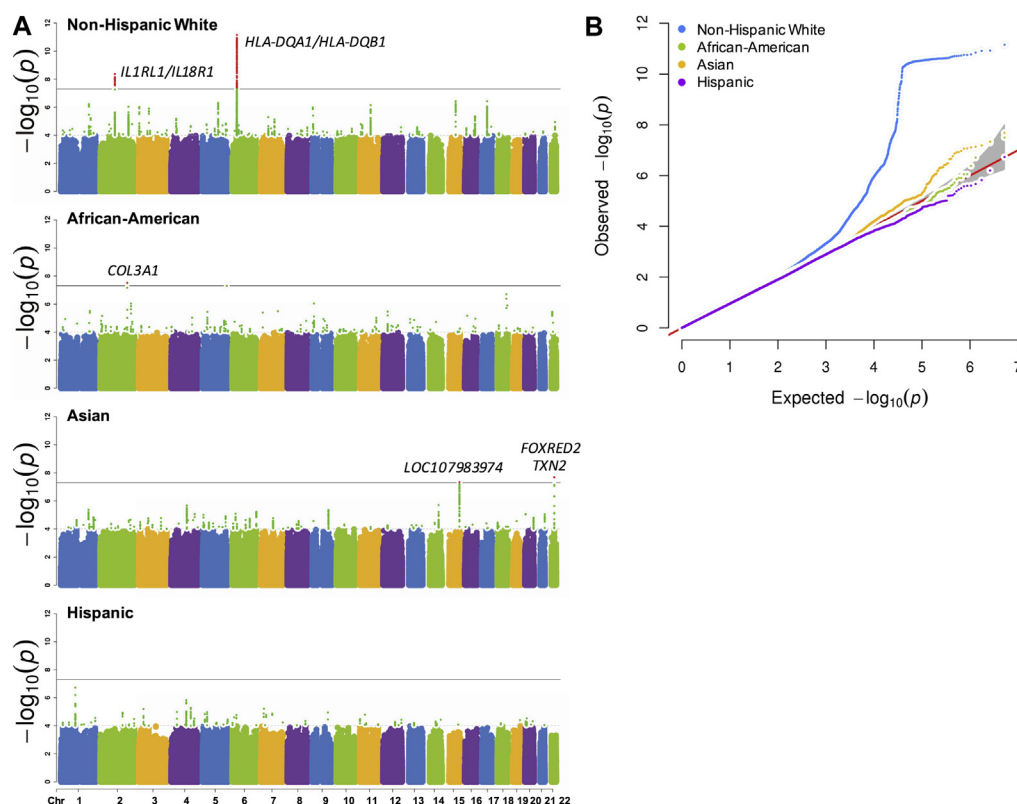


FIG 1. Discovery GWAS results for GERA populations. **A**, Manhattan plots for each GWAS are provided by racial/ethnic group, with chromosomal positions along the abscissa whereas $-\log(P)$ value is shown on the ordinate axis. Horizontal lines indicate significance thresholds for genome-wide (black line) and suggestive genome-wide associations (dashed line), respectively. **B**, Q-Q plot of results for each GWAS. For all populations, λ_{gc} values were 1.0 to 1.004.

genotyped in the GERA non-Hispanic white data set, of which 25 replicated at a Bonferroni-corrected P -value threshold of 4.42×10^{-04} . When the GERA SNP P values were combined with those of the cited NHGRI studies, 44 of 87 (51%) SNPs in 28 unique loci met the Bonferroni-corrected cutoff; of these, 25 SNPs in 16 loci met the traditional genome-wide significance threshold of $P < 5 \times 10^{-08}$ (see Table E2).

In the 3 additional racial/ethnic groups in GERA, 6.4 million to 12.7 million SNPs passed quality control and were evaluated by GWASs. Three SNPs (rs5756210 near FAD-dependent oxidoreductase domain containing 2 [*FOXRED2*], rs10534662 in thioredoxin 2 [*TXN2*], and rs8042955 in *LOC107983974/RP11-739G5.1*) achieved genome-wide significance in Asians, and rs13306275 in collagen type III alpha 1 chain (*COL3A1*) was genome-wide significant in African Americans (Fig 1, A; see Table E3 in this article's Online Repository at www.jacionline.org). No genome-wide significant or suggestive associations replicated for these groups in EVE, GABRIEL, or the NHGRI database. In addition, none of the associations approaching genome-wide significance overlapped with any genome-wide significant/suggestive SNP association across all 4 racial/ethnic groups.

We attempted to discern the potential functional relevance of the most highly significant genome-wide-significant SNPs. The top-ranked SNP in non-Hispanic whites was rs9272513, which is present in an intron of *HLA-DQA1* and is also an eQTL (expression quantitative trait loci) for both *HLA* loci and *IL1RL1/IL18R1* in the lung and circulation (see Table E4 in this article's Online Repository at www.jacionline.org). In addition, rs12712142 was associated with an 11% increased risk of asthma and is an eQTL for *IL1RL1*, reducing transcript expression in the lung (see Fig E1 in this article's Online Repository at www.jacionline.org). Further characterization of rs12712142, which was annotated to the 3'UTR region of *IL1RL1*, showed that it introduces a new binding site for hsa-miR-452-5p, which is also significantly upregulated in airway epithelia samples from those with asthma compared with samples from healthy, nonatopic controls (see Figs E2 and E3 in this article's Online Repository at www.jacionline.org). Because variations across multiple genes within affected pathways could directly impact asthma phenotypes, we analyzed 2143 suggestive ($P < 1 \times 10^{-05}$) associations from non-Hispanic whites in GERA for gene-set and tissue enrichment. Tissue and cell enrichment for relevant gene sets included those related to CD4⁺, CD8⁺, and B- and T-cell growth, morphology, and other activities, whereas 7 tissue enrichment sets included pathways for "T lymphocytes" and "CD4-Positive T lymphocytes" (see Table E5 in this article's Online Repository at www.jacionline.org).

Collectively, these analyses replicated previously reported top asthma GWAS findings as well as increased the significance threshold for many of these associations, in addition to expanding the list of novel SNPs that are strongly associated with asthma risk. Because of differences in GWAS study design, imputation, and available SNP data, most genome-wide significant SNPs from the discovery GWAS were not well represented in EVE or GABRIEL, limiting the total number of SNPs for replication. However, there was a moderate to high level of linkage disequilibrium between the top discovery GWAS SNPs not genotyped in GABRIEL or EVE and the replicated SNPs presented in Table I. Conditioning on the lead replicated SNP for chr6, rs17843604, reduced the strength of the regional GWAS association of *HLA-DQA1* (within 400 kb) to below

genome-wide significant levels (top SNP unadjusted P value = 7.5×10^{-07}) (see Fig E4 in this article's Online Repository at www.jacionline.org). Similarly, conditioning on rs1420101 removed all significant associations within 400 kb of the *IL1RL1/IL18R1* region. Finally, although we present novel GWAS findings from racial/ethnic groups in addition to non-Hispanic whites, our ability to replicate associations from these and other populations was limited, due in part to the aforementioned reasons. A recently conducted GWAS of adults and children with and without asthma also revealed novel associations in 6p21.31, 9p21.2, and 10q21.3 in European-Americans and 9q34.11 in African Americans, but we did not replicate these in our analysis of GERA.⁷ Nevertheless, like Almoguera et al,⁷ we did capture suggestive associations for established asthma susceptibility loci in individuals of European ancestry, including *ORMDL3/GSDMB*, *IL33*, and others.

The lack of overlap of asthma associations across the 4 ethnic groups in GERA may have more than one underlying explanation. One possibility is that we did not have sufficient statistical power to detect the same genetic associations across all racial/ethnic subgroups, due to variance in minor allele frequencies and lower sample sizes for the minority participants. However, differences in associations across racial/ethnic groups could also be attributed to unique biological pathways involved in asthma susceptibility in these populations. In Asians, asthma case status was associated with SNPs annotated to 2 oxidative stress pathway genes, *FOXRED2* and *TXN2*. Neither SNP was previously reported as associated with asthma in any population, and therefore could represent unique genetic risk factors in individuals of Asian ancestry. (Of note, the *FOXRED2* variant was not genotyped in African Americans, and therefore could not be tested in our GWAS). In Hispanics, we observed suggestive associations with asthma for 5 unique genes, including *TET2*, which is associated with chronic obstructive pulmonary disease phenotypes; again, none were previously associated with asthma risk. Finally, SNPs in collagen- and cadherin-related genes also showed potential relationships with asthma in African American subjects. Although other GWASs have reported associations between collagen⁸ and cadherin genes⁹ and asthma phenotypes, this is the first GWAS to specifically identify *COL25A1*, *COL3A1*, and *CDH7* as potential candidates.

In conclusion, previously unreported SNPs within the MHC II region of chromosome 6 and the *IL1RL1/IL18R1* region of chromosome 2 are associated with asthma susceptibility in adults of non-Hispanic white ancestry, whereas novel SNPs in *FOXRED2* and *TXN2* are associated with asthma in Asians, and *COL3A1* is associated with asthma in African Americans. One of the top associations, rs12712142, could confer a novel potential mechanism for asthma susceptibility through introduction of a new miRNA binding site that regulates the expression of *IL1RL1*. This study contributes novel associations with potential functional relevance for asthma susceptibility in older adults of diverse racial backgrounds, and represents one of the largest multiethnic GWASs of asthma to date.

We wish to acknowledge colleagues and investigators at Kaiser Permanente Northern California, University of California San Francisco, and Harvard Medical School for their support in providing access to the genotype data and study populations. We are grateful to the EVE Consortium, funded by RC2 HL101651, and to Dr Carole Ober, for generously providing us with their primary study results. This work was supported by the following grants from the National Institutes of Health: K01 HL130629, R01 HD085993 and U01 HL65899.

TABLE I. GWAS results for non-Hispanic whites

SNP	Chromosome	Location (bp)*	Gene	Minor allele*	Discovery (GERA)		Replication (GABRIEL)		Replication (EVE)		Combined P value
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	
rs17843604	6	32620283	HLA-DQA1	C	0.90 (0.88-0.93)	1.10×10^{-10}	0.86 (0.82-0.90)	1.68×10^{-10}	—	—	1.39×10^{-18}
rs17612633	6	32615710	HLA-DQA1	G	0.89 (0.87-0.93)	1.36×10^{-11}	0.87 (0.81-0.93)	4.07×10^{-05}	—	—	2.59×10^{-15}
rs1420101	2	102957716	IL1RL1	T	1.10 (1.06-1.13)	2.65×10^{-08}	1.11 (1.06-1.15)	9.60×10^{-07}	1.15 (1.06-1.25)	2.87×10^{-05}	8.25×10^{-15}
rs12998521	2	102974417	IL18R1	T	1.10 (1.06-1.13)	1.34×10^{-08}	1.11 (1.07-1.16)	1.39×10^{-07}	1.10 (1.01-1.20)	1.42×10^{-03}	3.05×10^{-14}
rs9272346	6	32604372	HLA-DQA1	G	0.89 (0.97-0.93)	1.13×10^{-11}	—	—	0.93 (0.85-1.00)	4.29×10^{-04}	1.50×10^{-12}
rs9272723	6	32609427	HLA-DQA1	T	0.89 (0.87-0.93)	2.52×10^{-11}	—	—	0.92 (0.85-1.00)	1.58×10^{-03}	4.46×10^{-12}
rs13019081	2	102950822	IL1RL1	C	1.11 (1.07-1.14)	2.09×10^{-09}	—	—	1.11 (1.02-1.22)	3.41×10^{-04}	3.28×10^{-10}
rs12712142	2	102960584	IL1RL1	A	1.01 (1.07-1.14)	4.65×10^{-09}	—	—	1.13 (1.05-1.23)	7.15×10^{-05}	5.94×10^{-10}
rs13001325	2	102939036	IL1RL1	T	1.11 (1.07-1.14)	3.49×10^{-09}	—	—	1.11 (1.02-1.22)	7.63×10^{-04}	6.43×10^{-10}
rs12479210	2	102949161	IL1RL1	T	1.11 (1.07-1.14)	4.32×10^{-09}	—	—	1.11 (1.02-1.22)	3.34×10^{-04}	6.98×10^{-10}
rs11123923	2	102967844	IL1RL1	A	1.10 (1.07-1.14)	3.89×10^{-09}	—	—	1.1 (1.01-1.2)	8.32×10^{-04}	7.30×10^{-10}
rs950880	2	102932562	IL1RL1	A	1.10 (1.07-1.14)	5.66×10^{-09}	—	—	1.11 (1.02-1.21)	1.88×10^{-04}	8.45×10^{-10}
rs6543119	2	102963072	IL1RL1	T	1.10 (1.06-1.13)	7.15×10^{-09}	—	—	1.14 (1.05-1.23)	1.23×10^{-04}	1.01×10^{-09}
rs13017455	2	102964742	IL1RL1	T	1.10 (1.06-1.13)	7.53×10^{-09}	—	—	1.14 (1.04-1.23)	2.50×10^{-04}	1.19×10^{-09}
rs2287037	2	102979028	IL1RL1	T	1.10 (1.06-1.13)	1.14×10^{-08}	—	—	1.10 (1.02-1.22)	6.01×10^{-03}	3.22×10^{-09}
rs9269080	6	32440969	HLA-DRB9	G	0.91 (0.9-0.95)	2.39×10^{-08}	—	—	0.94 (0.88-1.02)	.04	1.06×10^{-08}

Table shows the SNP identifiers, gene annotations, GWAS summary statistics and joint P values for GERA, GABRIEL and EVE.

*Chromosomal location and minor allele designations for GERA.

Amber Dahlin, PhD, MMSc^{a,*}

Joanne E. Sordillo, ScD^{b,*}

John Ziniti, MS^a

Carlos Iribarren, MD, MPH, PhD^c

Meng Lu, MD, MS^c

Scott T. Weiss, MD, MS^{a,d}

Kelan G. Tantisira, MD, MPH^{a,d}

Quan Lu, PhD^{e,f}

Mengyuan Ka, PhD^g

Blanca E. Himes, PhD^g

Eric Jorgenson, PhD^c

Ann Chen Wu, MD, MPH^{a,b}

From ^aChanning Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; ^bRecisOn Medicine Translational Research (PROMoTeR) Center, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Mass; ^cthe Division of Research, Kaiser Permanente Northern California, Oakland, Calif; ^dPartners Center for Personalized Medicine, Partners Health Care, Boston, Mass; ^eDepartments of ^fEnvironmental Health and ^gGenetics and Complex Diseases, Harvard T.H. Chan School of Public Health, Boston, Mass; ^hthe Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pa. E-mail: Ann.Wu@childrens.harvard.edu.

*These authors contributed equally to this study.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interests.

REFERENCES

1. Ferreira MA, McRae AF, Medland SE, Nyholt DR, Gordon SD, Wright MJ, et al. Association between ORMDL3, IL1RL1 and a deletion on chromosome 17q21 with asthma risk in Australia. *Eur J Hum Genet* 2011;19:458-64.

2. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363:1211-21.
3. Sleiman PM, Flory J, Imielinski M, Bradfield JP, Annaiah K, Willis-Owen SA, et al. Variants of DENND1B associated with asthma in children. *N Engl J Med* 2010;362:36-44.
4. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet* 2011;43:887-92.
5. Banda Y, Kvale MN, Hoffmann TJ, Hesselton SE, Ranatunga D, Tang H, et al. Characterizing race/ethnicity and genetic ancestry for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics* 2015;200:1285-95.
6. Kvale MN, Hesselton S, Hoffmann TJ, Cao Y, Chan D, Connell S, et al. Genotyping informatics and quality control for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics* 2015;200:1051-60.
7. Almoquera B, Vazquez L, Mentch F, Connolly J, Pacheco JA, Sundaresan AS, et al. Identification of four novel loci in asthma in European American and African American populations. *Am J Respir Crit Care Med* 2017;195:456-63.
8. Duan QL, Lasky-Su J, Himes BE, Qiu W, Litonjua AA, Damask A, et al. A genome-wide association study of bronchodilator response in asthmatics. *Pharmacogenomics J* 2014;14:41-7.
9. McGeachie MJ, Wu AC, Tse SM, Clemmer GL, Sordillo J, Himes BE, et al. CTNNA3 and SEMA3D: promising loci for asthma exacerbation identified through multiple genome-wide association studies. *J Allergy Clin Immunol* 2015;136:1503-10.

<https://doi.org/10.1016/j.jaci.2018.11.037>

Large-scale, multi-ethnic genome-wide association study identifies novel loci contributing to asthma susceptibility in adults

Amber Dahlin, Joanne E. Sordillo, John Ziniti, Carlos Iribarren, Meng Lu, Scott T. Weiss, Kelan G.

Tantisira, Quan Lu, Mengyuan Kan, Blanca E. Himes, Eric Jorgenson, Ann Chen Wu

Supplement

- I. Methods**
- II. Conflict of Interest Statement**
- III. Acknowledgement**
- IV. References**

I. METHODS

A. Study populations and phenotyping

Kaiser Permanente Northern California (KPNC) Genetic Epidemiology Research on Adult Health and Aging Cohort (GERA)

The Research Program on Genes, Environment, and Health (RPGEH) GERA cohort includes electronic medical record and genotype information for 110,266 adult male and female members of the Kaiser Permanente Medical Care Plan. Sample collection and genotyping of the GERA population (dbGaP: phs000674.v1.p1) were previously described¹⁻³. Electronic medical records and survey information from the GERA population were searched to select adult patients of at least 21 years of age. All races/ethnicities were self-reported. Asthma cases were defined as patients with one or more of the following electronic medical record entries: physician-diagnosed asthma, self-reported asthma, or a report of an asthma exacerbation (hospitalization, ICU/emergency department visit due to asthma); in contrast, controls (non-asthmatics) had negative reports (“0” or “No/None”) for all of the aforementioned records. Exclusion criteria included the following comorbidities: COPD, pulmonary embolism, primary pulmonary hypertension, cystic fibrosis, and bronchiectasis. Controls

were then selected from the remaining non-asthmatic patients within each of the racial/ethnic groups at a ratio of 2-4 controls per case, using the R package *dplyr*⁴. After excluding subjects with comorbidities, 16,274 cases and 38,269 controls of non-Hispanic European American/white ancestry, 1,300 cases and 4,927 controls of Asian ancestry, 1,320 cases and 4,007 controls of Hispanic ancestry, and 611 cases and 1,915 controls of African-American ancestry remained for analysis. Clinical and demographic information for the GERA asthma cases and controls analyzed in this study is summarized in **Table 1**.

EVE

Genome-wide genotypes and summary statistics from the EVE Consortium^{5,6} were a primary replication population for the GWAS. GWAS data including SNP annotations, association test statistics and related information were previously reported and were used for replication of GERA discovery GWAS results⁵.

GABRIEL

The European GABRIEL Consortium investigated 10,365 asthmatic cases and 16,110 population-matched controls from 23 different studies evaluating non-Hispanic whites⁷. Data including SNP annotations, association test statistics and related information were downloaded from the GABRIEL Consortium repository (<http://www.cng.fr/gabriel/index.html>) and used for direct replication of discovery GWAS results for non-Hispanic white GERA subjects.

NHGRI Catalog of Published GWAS

GWAS results with strong previously published evidence of association with asthma were downloaded from NHGRI Catalog of Published Genome-Wide Association Studies (<https://www.genome.gov/gwastudies/>). In all, 113 SNPs were suggestive ($P < 1 \times 10^{-5}$) across >30 NHGRI studies of asthma, and/or asthma/allergy or asthma/COPD. In GERA, 87 of these 113 SNPs were present (genotyped) and were investigated for replication.

B. Genotyping and Quality Control Procedures

Genotyping of DNA extracted from saliva samples of patients participating in the KPNC Biobank was performed using race/ethnicity specific Affymetrix Axiom arrays as previously described.^{8,9} As described previously², for GERA, approximately 94% of samples and more than 98% of genetic markers passed after stringent QC was performed on an array-wise basis, with an initial genotyping call rate $\geq 97\%$, allele frequency difference ≤ 0.15 between males and females for autosomal markers, and genotype concordance rate > 0.75 across duplicate genetic markers. For both studies, consistency with reported ethnicity was determined using principal components analysis (PCA) using EIGENSTRAT v3.0 and cluster analysis. All additional QC procedures were performed using PLINK v.1.94 (<https://www.cog-genomics.org/plink2>).

C. Imputation

Imputation for GERA was previously reported². Prior to imputation, genetic markers with a minor allele frequency (MAF) $< 1\%$, or a genotype call rate $< 90\%$ were excluded as described². Genotypes were pre-phased with Shape-IT v2.5 and genetic markers were imputed to 1000 Genomes Project (phase 1 integrated release) reference CEU panels using IMPUTE2. Imputation procedures for minority race-specific genotype data have been previously described⁹.

D. GWAS Input Data

Prior to GWAS, a threshold for imputed SNPs was applied to exclude SNPs with imputation quality scores < 0.9 and MAF $< 1\%$. A final set of 7,230,512 SNPs in 16,274 non-Hispanic white cases and 38,269 non-Hispanic white controls (54,543 individuals) passed genotype and sample quality control filters including minor allele frequency $> 1\%$ and HWE $< 10^{-05}$. Correspondingly, 6,389,101 SNPs in 1,300 Asian cases and 4,927 Asian controls (6,227 individuals) passed the same quality control filtering procedures, as did 7,735,858 SNPs in 1,320 Hispanic cases and 4,007 Hispanic controls (5,327 individuals), and 12,660,172 SNPs in 611 in African American cases and 1915 in African American controls (2,526 individuals).

E. Statistical analysis

Covariate-adjusted logistic regression of asthma status, specifying an additive genetic model, was performed using PLINKv.1.9¹⁰. For GERA, covariates included: age (at time of enrollment survey), gender, BMI, smoking status (never smoked, past smoker, current smoker), length of follow-up (years of longitudinal electronic medical record data), and the first six principal components obtained from ancestry-based PCA, as described above. Summary statistics and Odds ratios with 95% confidence intervals were then obtained for each SNP, and P values were adjusted using genomic control, specifying a Bonferroni correction threshold for GWAS of $P < 5 \times 10^{-08}$. SNPs with P values below 5×10^{-08} were considered genome-wide significant while those with P values below 10^{-05} were suggestive of genome-wide significance. SNPs that were common (genotyped) to GERA and a replication study (EVE or GABRIEL) and that also met genome-wide significance in GERA were then evaluated for replication. Association test statistics for these SNPs were then compared to determine whether a given SNP met an experiment-wide significance threshold and also had a concordant direction of effect in both studies. Joint P-values for replicated SNPs were obtained using a weighted Z-score approach. SNPs of interest were annotated to genes using the Bioconductor package *VariantAnnotation*¹¹ and specifying hg19 as the reference catalog to infer SNP base type.

F. Gene annotation and pathway enrichment analyses

DEPICT¹² was used to annotate SNPs to genes and perform tissue-based, gene set-based and pathway-based enrichment analyses. DEPICT uses association information to prioritize genes based on LD structure and known biological relationships⁴². DEPICT was used to construct and prioritize loci, and perform gene set and tissue enrichment analyses using the replicated genetic association summary statistics. To run DEPICT, the configuration file was changed to specify an association P-value cutoff of 1×10^{-05} , include up to 25 genes within a cluster, use 1000 Genomes Project genotype data for annotation, complete 50 repetitions to compute FDR, run 500 permutations, and set a

background GWAS clumping P-value of 0.005. All other DEPICT settings were unchanged from the original configuration file.

G. eQTL analysis

The publically available Gene and Tissue Expression (GTEx) Portal

(<http://www.gtexportal.org/home/>) was mined to determine whether any of our top SNP hits (those identified as significantly associated with asthma status in GERA and/or at least one of the two replication populations (EVE or GABRIEL)) are classified as cis- or trans-eQTLs. All tissues present in the GTEx database were screened for potential tissue-specific single and multi-tissue eQTLs and splice eQTLs. A table and boxplots of gene expression by genotype were generated for significant eQTLs in relevant tissues (lung, whole blood, EBV-transformed lymphocytes).

H. Bioinformatic analyses

The predicted functional consequences of SNPs based on their annotations within genes (e.g. intronic, coding, missense) was performed using SNPnexus¹³. The effect of SNPs on microRNA (miRNA) binding sites were also investigated using miRNASNPv2.0 (<http://bioinfo.life.hust.edu.cn/miRNASNP2/index.php>). Differential expression profiles were generated using Affymetrix Human Genome U133A Array data available in the Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>).

II. **CONFLICT OF INTEREST STATEMENT.** The authors have no competing interests to declare.

III. **ACKNOWLEDGEMENTS.** We thank colleagues and investigators at Kaiser Permanente Northern California, University of California San Francisco, and Harvard Medical School for

their support in providing access to the genotype data and study populations. We are grateful to the EVE Consortium, funded by RC2 HL101651, and Dr. Carole Ober, for generously providing us with their primary study results. This work was supported by K01 HL130629 (to A.D.), and U01 HL65899 (to S.T.W. and K.G.T.).

IV. SUPPLEMENTAL REFERENCES

1. Banda Y, Kvale MN, Hoffmann TJ, et al. Characterizing Race/Ethnicity and Genetic Ancestry for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics*. 2015;200(4):1285-1295.
2. Kvale MN, Hesselton S, Hoffmann TJ, et al. Genotyping Informatics and Quality Control for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics*. 2015;200(4):1051-1060.
3. Lapham K, Kvale MN, Lin J, et al. Automated Assay of Telomere Length Measurement and Informatics for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics*. 2015;200(4):1061-1072.
4. *dplyr: A Grammar of Data Manipulation*. [computer program]. Version R package version 0.4.12015.
5. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *The New England journal of medicine*. 2010;363(13):1211-1221.
6. Torgerson DG, Ampleford EJ, Chiu GY, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet*. 2011;43(9):887-892.
7. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med*. 2010;363(13):1211-1221.
8. Hoffmann TJ, Kvale MN, Hesselton SE, et al. Next generation genome-wide association tool:

- design and coverage of a high-throughput European-optimized SNP array. *Genomics*. 2011;98(2):79-89.
9. Hoffmann TJ, Zhan Y, Kvale MN, et al. Design and coverage of high throughput genotyping arrays optimized for individuals of East Asian, African American, and Latino race/ethnicity using imputation and a novel hybrid SNP selection algorithm. *Genomics*. 2011;98(6):422-430.
 10. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81(3):559-575.
 11. Obenchain V, Lawrence M, Carey V, Gogarten S, Shannon P, Morgan M. VariantAnnotation: a Bioconductor package for exploration and annotation of genetic variants. *Bioinformatics*. 2014;30(14):2076-2078.
 12. Pers TH, Karjalainen JM, Chan Y, et al. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat Commun*. 2015;6:5890.
 13. Dayem Ullah AZ, Lemoine NR, Chelala C. SNPnexus: a web server for functional annotation of novel and publicly known genetic variants (2012 update). *Nucleic Acids Res*. 2012;

Large-scale genome-wide association study identifies novel loci contributing to asthma susceptibility in adults

Amber Dahlin, Joanne E. Sordillo, John Ziniti, Carlos Iribarren, Meng Lu, Scott T. Weiss, Kelan G. Tantisira, Quan Lu, Mengyuan Kan, Blanca E. Himes, Eric Jorgenson, Ann Chen Wu

Supplement

- I. Supplemental Tables 1-4**
- II. Supplemental Figure Legends 1-4**
- III. Supplemental Figures 1-4**

II. SUPPLEMENTAL TABLES

Supplemental Table 1. Demographic Information for GERA Populations.

Variable	Non-Hispanic Whites			Asians			Hispanics			African Americans		
	Asthma Cases	Non-Asthmatic Controls	P Value	Asthma Cases	Non-Asthmatic Controls	P Value	Asthma Cases	Non-Asthmatic Controls	P Value	Asthma Cases	Non-Asthmatic Controls	P Value
Sample Size (N)	16,274	38,269		1300	4927		1320	4007		611	1915	
Age in yrs. Mean (range)	63.7 (18-90)	64.6 (18-90)	<0.001	54.5 (19-89)	54.8 (19-89)	0.35	54.3 (19-90)	54.3 (19-88)	0.88	56.6 (19-90)	58 (19-90)	0.02
% Male	36%	43%	<0.001	39%	42%	0.02	31%	40%	<0.001	34%	45%	<0.001
BMI mean (range)	28.5 (13-71)	27 (12-77)	<0.001	25.5 (13-54)	24.2 (15-50)	<0.001	29.2 (14-58)	27.5 (16-75)	<0.001	30.6 (14-58)	28.7 (17-57)	<0.001
Comorbidities :												
Allergic rhinitis	5442 (33%)	6113 (16%)	<0.001	523(40%)	956 (19%)	<0.001	560 (42%)	824 (21%)	<0.001	234 (38%)	359 (19%)	<0.001
Congestive Heart Failure	501 (3%)	931 (2%)	<0.001	28 (2%)	51 (1%)	0.001	23 (2%)	51 (1%)	0.21	22 (4%)	55 (3%)	0.36
GERD	4028 (25%)	6334 (17%)	<0.001	206 (16%)	615 (12%)	0.001	369 (28%)	728 (18%)	<0.001	157 (26%)	322 (17%)	<0.001
Acute respiratory infections	8539 (52%)	13978 (37%)	<0.001	635 (49%)	1690 (34%)	<0.001	779 (59%)	1777 (44%)	<0.001	329 (54%)	747 (39%)	<0.001
Chronic upper respiratory infections	2937 (18%)	3702 (10%)	<0.001	186 (14%)	385 (8%)	<0.001	236(18%)	403 (10%)	<0.001	131 (21%)	173 (9%)	<0.001
Allergies	11528 (71%)	19335 (51%)	<0.001	974 (75%)	2713 (55%)	<0.001	975 (74%)	1934 (48%)	<0.001	434 (71%)	878 (46%)	<0.001
Smoking Status:												
Never	8717 (54%)	21302 (56%)	<0.001	946 (73%)	3725 (76%)	<0.001	838 (63%)	2591(65%)	0.68	359 (59%)	1113(58%)	0.07
Former	6271 (39%)	13869 (36%)		327 (25%)	1007 (20%)		409 (31%)	1190 (30%)		215 (39%)	631 (33%)	
Current	703 (4%)	1548 (4%)		27 (2%)	195 (4%)		73 (6%)	226 (6%)		37 (6%)	171(9%)	

Supplemental Table 2. List of Replicated Loci from NHGRI Catalog of Published Asthma GWAS

SNP	GERA GWAS						NHGRI Published GWAS of Asthma						Joint P-value
	Chr.	Chr. Pos.	Minor Allele	OR	P-Value	Region	Chr. Pos.	Locus	Risk Allele	P Value	OR/ Beta	PubMed ID	
rs1837253	5	110401872	T	0.92	4.38E-06	5q22.1	111066174	<i>TSLP</i>	C	1.00E-16	1.17	21804548	1.34E-16
rs204993	6	32155581	G	1.09	3.62E-06	6p21.32	32187804	<i>PBX2</i>	A	2.00E-15	1.17	21804548	5.18E-16
rs11078927	17	38064405	T	0.92	6.59E-07	17q21.1	39908152	<i>GSDMB</i>	?	2.00E-16	NA	21804549	4.32E-13
rs9272346	6	32604372	G	0.89	1.13E-11	6p21.32	32636595	<i>HLA-DQA1</i>	?	2.00E-08	NA	23181788	8.41E-13
rs3117098	6	32358513	G	0.93	8.49E-05	6p21.32	32390736	<i>BTNL2</i>	G	5.00E-12	1.16	21804548	3.84E-12
rs10508372	10	8972018	A	0.91	1.42E-03	10p14	8930055	<i>LOC338591</i>	C	2.00E-15	1.16	21804548	6.93E-12
rs1438673	5	110467499	T	0.92	1.41E-06	5q22.1	111131801	<i>WDR36</i>	C	3.00E-11	1.16	24388013	1.00E-11
rs2305480	17	38062196	A	0.92	5.04E-07	17q21.1	39905943	<i>GSDMB</i>	G	1.00E-07	1.18	20860503	1.28E-11
rs3771166	2	102986222	A	0.92	2.27E-06	2q12.1	102369762	<i>IL18R1</i>	G	3.00E-09	1.15	20860503	1.33E-11
rs1837253	5	110401872	T	0.92	4.38E-06	5q22.1	111066174	<i>TSLP</i>	?	1.00E-14	NA	21804549	1.73E-11
rs9500927	6	32961361	A	1.1	2.20E-05	6p21.32	32993584	<i>HLA-DOA</i>	T	4.00E-09	1.13	21804548	2.75E-11
rs1701704	12	56412487	G	1.06	1.31E-03	12q13.2	56018703	<i>IKZF4</i>	G	2.00E-13	1.19	21804548	5.38E-11
rs13408661	2	102955082	A	0.91	8.34E-05	2q12.1	102338622	<i>IL18R1/IL1RL1</i>	G	1.00E-09	1.23	23028483	9.89E-11
rs1837253	5	110401872	T	0.92	4.38E-06	5q22.1	111066174	<i>TSLP</i>	C	1.00E-09	1.17	24388013	1.59E-10
rs1342326	9	6190076	C	1.1	7.89E-06	9p24.1	6190076	<i>IL33</i>	C	9.00E-10	1.2	20860503	3.77E-10
rs72699186	9	6175855	T	1.1	9.21E-06	9p24.1	6175855	<i>IL33</i>	T	2.00E-09	1.26	24388013	5.40E-10
rs3771180	2	102953617	T	0.91	8.53E-05	2q12.1	102337157	<i>IL1RL1</i>	?	2.00E-15	NA	21804549	7.80E-10
rs744910	15	67446785	G	1.07	4.84E-05	15q22.33	67154447	<i>SMAD3</i>	G	4.00E-09	1.12	20860503	8.40E-10
rs7775228	6	32658079	C	1.05	2.19E-02	6p21.32	32690302	<i>HLA-DQB1</i>	A	5.00E-15	1.17	21804548	2.02E-09
rs10197862	2	102966549	G	0.91	7.75E-05	2q12.1	102350089	<i>IL1RL1</i>	A	4.00E-11	1.24	24388013	2.47E-09
rs9268516	6	32379489	T	1.06	4.65E-04	6p21.32	32411712	<i>HLA-DRA</i> ,	T	1.00E-08	1.15	23028483	3.87E-09
rs62026376	16	11228712	T	0.93	4.12E-05	16p13.13	11134855	<i>CLEC16A</i>	C	1.00E-08	1.17	24388013	6.85E-09
rs2381416	9	6193455	C	1.07	1.60E-04	9p24.1	6193455	<i>IL33</i>	?	2.00E-12	NA	21804549	1.09E-08
rs3129943	6	32338695	G	1.03	5.51E-02	6p21.32	32370918	<i>C6orf10</i>	T	3.00E-15	1.17	21804548	1.31E-08
rs2305480	17	38062196	A	0.92	5.04E-07	17q21.1	39905943	<i>GSDMB</i>	G	6.00E-23	1.32	24241537	1.51E-08
rs7216389	17	38069949	C	0.93	7.61E-06	17q21.1	39913696	<i>ORMDL3</i>	T	9.00E-11	1.45	17611496	1.05E-07
rs3129890	6	32414273	C	1.03	5.65E-02	6p21.32	32446496	<i>HLA-DRA</i>	T	5.00E-13	1.15	21804548	1.05E-07
rs7686660	4	144003159	G	1.03	5.35E-02	4q31.21	143082006	<i>LOC729675</i>	T	2.00E-12	1.16	21804548	1.62E-07
rs7130588	11	76270683	G	1.09	1.22E-06	11q13.5	76559639	<i>LRRC32</i>	G	2.00E-08	1.09	21907864	2.36E-07
rs9807989	2	102971200	C	0.93	5.66E-06	2q12.1	102354740	<i>IL18R1, IL1RL1</i>	?	6.00E-08	1.33	22561531	4.11E-07

rs3894194	17	38121993	A	1.05	4.06E-03	17q21.1	39965740	GSDMA	A	5.00E-09	1.17	20860503	5.20E-07
rs7212938	17	38122680	G	1.05	2.69E-03	17q21.1	39966427	GSDMA	G	4.00E-10	1.16	24388013	8.41E-07
rs343496	9	6068077	T	0.93	5.59E-04	9p24.1	6068077	RANBP6	T	2.00E-06	1.14	24388013	1.39E-06
rs2069408	12	56364321	G	1.03	7.51E-02	12q13.2	55970537	CDK2	C	1.00E-10	1.15	21804548	1.65E-06
rs1295686	5	131995843	T	1.05	6.75E-03	5q31.1	132660151	IL13	T	1.00E-07	1.15	20860503	3.52E-06
rs12450323	17	37972708	T	1.05	4.75E-03	17q21.1	39816455	IKZF3	T	4.00E-07	1.16	24388013	1.45E-05
rs10197862	2	102966549	G	0.91	7.75E-05	2q12.1	102350089	IL18R1/IL1RL1	?	2.00E-06	1.99	26620591	2.53E-05
rs928413	9	6213387	G	1.07	1.85E-04	9p24.1	6213387	IL33	G	9.00E-13	1.24	24241537	2.80E-05
rs4794820	17	38089344	A	0.95	8.06E-04	17q21.1	39933091	ORMDL3	?	1.00E-08	1.33	22561531	9.40E-05
rs11071559	15	61069988	T	0.96	5.40E-02	15q22.2	60777789	RORA	C	1.00E-07	1.18	20860503	1.01E-04
rs3853750	5	110154309	C	1.05	2.04E-02	5q22.1	110818610	SLC25A46	C	2.00E-07	1.15	24388013	1.01E-04
rs7009110	8	81291879	T	1.03	3.98E-02	8q21.13	80379644	ZBTB10	T	4.00E-09	1.14	24388013	1.11E-04
rs3119939	13	63638329	C	1.01	2.39E-01	13q21.31	63064196	PCDH20	?	8.00E-06	1.08	21907864	1.31E-04
rs2073643	5	131723288	T	1.03	7.28E-02	5q31.1	132387596	SLC22A5	T	2.00E-07	1.11	20860503	2.14E-04
rs6503525	17	38095174	C	1.05	1.04E-03	17q21.1	39938921	ORMDL3	C	5.00E-07	1.33	21150878	4.37E-04
rs3805236	4	144357737	A	1.01	3.03E-01	4q31.21	143436584	GAB1	G	7.00E-08	1.12	21804548	5.15E-04
rs3894194	17	38121993	A	1.05	4.06E-03	17q21.1	39965740	GSDMA	A	3.00E-21	1.59	24241537	5.27E-04
rs6871536	5	131969874	C	1.06	2.70E-03	5q31.1	132634182	RAD50	C	8.00E-07	1.17	24241537	9.67E-04
rs2244012	5	131901225	G	1.06	2.81E-03	5q31.1	132565533	RAD50	C	3.00E-07	1.64	20159242	1.43E-03
rs987870	6	33042880	G	1.06	7.42E-03	6p21.32	33075103	HLA-DPB1	C	2.00E-10	1.4	21814517	2.47E-03
rs7521681	1	108322535	A	1.03	1.26E-01	1p13.3	107779913	VAV3	A	7.00E-07	1.15	24388013	2.65E-03
rs76043829	2	218677586	A	0.97	1.30E-01	2q35	217812863	TNS1	A	6.00E-07	1.21	24388013	2.71E-03
rs1295686	5	131995843	T	1.05	6.75E-03	5q31.1	132660151	IL13	T	2.00E-06	1.31	24241537	2.75E-03
rs6982751	8	10813474	G	0.98	1.57E-01	8p23.1	10955964	XKR6	G	4.00E-07	1.19	24388013	3.49E-03
rs1588265	5	59369794	G	0.99	3.03E-01	5q12.1	60073967	PDE4D	C	3.00E-08	1.18	19426955	3.61E-03
rs6867913	5	141445980	A	0.96	1.52E-02	5q31.3	142066415	NDFIP1	?	4.00E-06	1.33	22561531	4.28E-03
rs9866261	3	64526567	G	0.95	2.11E-02	3p14.1	64540891	ADAMTS9	G	1.00E-07	1.45	26620591	9.63E-03
rs11214966	11	114231255	C	1.02	2.45E-01	11q23.2	114360533	C11orf71	?	6.00E-07	NA	21804549	1.46E-02
rs41295115	10	6124621	C	0.99	3.56E-01	10p15.1	6082658	RBM17,	C	5.00E-07	1.28	24388013	1.85E-02
rs4845783	1	152492559	G	1.01	2.38E-01	1q21.3	152520083	CRCT1	?	6.00E-06	NA	21804549	2.00E-02
rs2786098	1	197325908	T	1.02	1.88E-01	1q31.3	197356778	DENND1B, CRB1	?	2.00E-13	NA	20032318	2.02E-02
rs72766477	5	83907229	A	0.99	4.05E-01	5q14.3	84611411	EDIL3	A	5.00E-07	1.34	24388013	2.47E-02
rs3019885	8	118025645	G	1.03	6.35E-02	8q24.11	117013406	SLC30A8	G	5.00E-13	1.34	21814517	2.53E-02
rs2786098	1	197325908	T	1.02	1.88E-01	1q31.3	197356778	DENND1B, CRB1	?	9.00E-11	1.43	20032318	2.83E-02
rs6517368	21	38007943	C	1	4.01E-01	21q22.13	36635645	SIM2	C	2.00E-06	1.12	24388013	3.03E-02
rs2544523	2	15920323	T	1.01	2.15E-01	2p24.3	15780199	MYCN, DDX1	T	1.00E-06	1.07	24993907	3.26E-02
rs17605016	12	62250420	G	0.99	4.26E-01	12q14.1	61856639	FAM19A2	G	2.00E-06	1.19	24388013	3.47E-02
rs9534578	13	47843377	A	0.98	2.52E-01	13q14.2	47269242	GNG5P5	?	2.00E-07	1.06	24993907	3.61E-02

rs17525472	15	51969668	C	1.04	8.02E-02	15q21.2	51677471	SCG3	?	2.00E-06	NA	20159242	5.46E-02
rs10521233	17	13559080	G	1.04	1.23E-01	17p12	13655763	NR	G	3.00E-06	0.14	22560479	7.60E-02
rs2705520	3	112269287	A	0.92	1.73E-01	3q13.2	112550440	ATG3	?	2.00E-06	NA	23829686	7.65E-02
rs6967330	7	105658451	A	1.02	1.86E-01	7q22.3	106018005	CDHR3	A	3.00E-14	1.26	24241537	8.10E-02
rs16929097	9	12521826	A	0.96	2.17E-01	9p23	12521826	intergenic	?	8.00E-09	NA	23829686	8.36E-02
rs2473967	6	113479335	G	0.97	2.23E-01	6q21	113158133	intergenic	?	2.00E-06	NA	23829686	1.06E-01
rs9297216	8	34045261	T	0.98	2.66E-01	8p12	34187743	intergenic	?	1.00E-06	NA	23829686	1.30E-01
rs10043228	5	115597048	T	1	4.76E-01	5q23.1	116261351	COMMD10	T	4.00E-06	1.32	24993907	1.43E-01
rs11745587	5	131796922	A	1.01	2.95E-01	5q31.1	132461230	C5orf56	?	2.00E-06	1.26	22561531	1.52E-01
rs7927044	11	127761666	A	0.94	2.51E-01	11q24.2	127891771	NR	A	7.00E-09	0.16	22560479	1.55E-01
rs7922491	10	53493473	A	1.02	2.89E-01	10q21.1	51733713	PRKG1	A	5.00E-07	1.13	21907864	1.97E-01
rs4129267	1	154426264	T	1.01	3.02E-01	1q21.3	154453788	IL6R	T	2.00E-08	1.09	21907864	1.97E-01
rs4815617	20	3827309	T	1.02	2.56E-01	20p13	3846662	KIAA1271	?	8.00E-06	NA	20159242	2.00E-01
rs11141597	9	89527458	G	0.99	4.60E-01	9q21.33	86912543	intergenic	?	2.00E-06	NA	23829686	2.77E-01
rs2378383	9	82039362	G	0.99	3.03E-01	9q21.31	79424447	TLE4,	?	7.00E-07	1.64	19714205	2.85E-01
rs10970976	9	32433526	C	1	4.97E-01	9p21.1	32433528	ACO1	?	4.00E-06	1.28	22561531	3.14E-01
rs9815663	3	3614887	T	1	4.66E-01	3p26.2	3573203	IL5RA	T	2.00E-08	0.17	22560479	3.38E-01
rs6456042	6	166534742	A	0.99	3.63E-01	6q27	166121254	T	?	6.00E-06	NA	22538805	3.50E-01
rs7328278	13	36351766	C	1	4.80E-01	13q13.3	35777629	NR	C	3.00E-06	0.13	22560479	3.73E-01

Supplemental Table 3. Genome Wide Association Study Results for Non-White Groups in GERA.

Asians (N=6,227;1300 asthma cases; 4927 controls)					
SNP	Chr.	Gene/ Nearest Gene	Minor Allele	OR	P Value
rs5756210	22	<i>FOXRED2</i>	T	1.47 (1.29, 1.68)	6.50 x10 ⁻⁰⁹
rs10534662	22	<i>TXN2</i>	A	1.46 (1.28, 1.66)	2.08 x10 ⁻⁰⁸
rs8042955	15	<i>RP11-739G5.1*/</i> <i>LOC107983974</i>	A	0.72 (0.65, 0.81)	4.61 x10 ⁻⁰⁸
rs7350795	15	<i>RP11-739G5.1*/</i> <i>LOC107983974</i>	C	0.74 (0.66, 0.82)	6.48 x10 ⁻⁰⁸
rs2011106	22	<i>FOXRED2</i>	C	1.43 (1.26, 1.63)	7.21 x10 ⁻⁰⁸
rs5756219	22	<i>FOXRED2</i>	A	1.45 (1.27, 1.68)	7.49 x10 ⁻⁰⁸
rs4777933	15	<i>RP11-739G5.1*/</i> <i>LOC107983974</i>	G	0.74 (0.66, 0.83)	7.77 x10 ⁻⁰⁸
rs4528520	15	<i>RP11-739G5.1/</i> <i>LOC107983974</i>	G	0.74 (0.66, 0.83)	8.45 x10 ⁻⁰⁸
rs3900806	22	<i>FOXRED2</i>	T	1.43 (1.25, 1.63)	8.45 x10 ⁻⁰⁸
rs4074327	15	<i>RP11-739G5.1*/</i> <i>LOC107983974</i>	A	0.73 (0.65, 0.82)	1.07 x10 ⁻⁰⁷
Hispanics (N=5,327; 1,320 asthma cases, 4,007 controls)					
rs144484929	1	<i>COL11A1</i>	C	1.84 (1.46, 2.31)	1.87x10 ⁻⁰⁷
rs72681220	1	<i>COL11A1</i>	T	1.77 (1.42, 2.22)	6.35x10 ⁻⁰⁷
rs55789739	1	<i>COL11A1</i>	C	1.90 (1.48, 2.45)	6.76x10 ⁻⁰⁷
rs2088484	4	<i>TET2</i>	C	0.60 (0.49, 0.74)	1.52 x10 ⁻⁰⁶
rs12642165	4	<i>TET2</i>	G	0.61 (0.50, 0.75)	2.17x10 ⁻⁰⁶
rs79551278	4	<i>TET2</i>	G	0.60 (0.49, 0.75)	2.48 x10 ⁻⁰⁶
chr4:106209690:I	4	<i>TET2</i>	I	0.63 (0.52, 0.77)	2.53 x10 ⁻⁰⁶
rs140336054	1	<i>COL11A1</i>	T	1.87 (1.44, 2.43)	2.60 x10 ⁻⁰⁶
rs180803027	1	<i>COL11A1</i>	A	1.74 (1.38, 2.20)	2.69 x10 ⁻⁰⁶
rs186407539	1	<i>COL11A1</i>	C	1.68 (1.35, 2.10)	3.19 x10 ⁻⁰⁶
African Americans (N=2,526; 611 asthma cases, 1,915 asthma controls)					
rs13306275	2	<i>COL3A1</i>	G	2.13 (1.63, 2.78)	3.10 x10 ⁻⁰⁸
rs702072	5	<i>SMIM23</i>	A	1.91 (1.51, 2.41)	5.06 x10 ⁻⁰⁸

rs1516454	2	<i>COL3A1</i>	G	2.20 (1.65, 2.93)	6.91 x10 ⁻⁰⁸
rs1484711	18	<i>CDH7</i>	T	1.75 (1.42, 2.16)	1.96 x10 ⁻⁰⁷
rs72944064	18	<i>CDH7</i>	C	1.75 (1.41,2.17)	4.14x10 ⁻⁰⁷
rs2083125	2	<i>FN1</i>	G	0.65 (0.54,0.77)	8.29 x10 ⁻⁰⁷
rs7847733	9	<i>TYRP1</i>	T	1.48 (1.27,1.74)	8.86 x10 ⁻⁰⁷
rs12105865	2	<i>LOC102724849*</i>	C	0.65 (0.54,0.77)	8.93 x10 ⁻⁰⁷
rs116311307	16	<i>TMEM114</i>	C	2.92 (1.90, 4.47)	9.29 x10 ⁻⁰⁷
rs78218566	16	<i>TMEM114</i>	A	2.92 (1.90, 4.47)	9.29 x10 ⁻⁰⁷

Table shows the top 10 SNP associations (lowest P values) from self-reported racial/ethnic groups. In column 3, the nearest gene within 50KB of the given SNP is provided.

*Non-coding RNA

Supplemental Table 4. Gene-set and tissue enrichment of suggestive associations

Top 10 Enriched Gene Sets			Top 10 Enriched Tissues				
Original gene set ID	Original gene set description	Nominal P value	MeSH term	MeSH first level term	MeSH second level term	Name	Nominal P value
ENSG00000182481	KPNA2 PPI subnetwork	7.11E-06	A11.118.637.555.567.569	Cells	Blood Cells	T Lymphocytes	0.02
ENSG00000215769	ENSG00000215769 PPI subnetwork	7.11E-06	A15.145.229.637.555.567.569.200	Hemic and Immune Systems	Blood	CD4 Positive T Lymphocytes	0.02
MP:0004351	short humerus	1.97E-04	A11.118.637.555.567.569.200.700	Cells	Blood Cells	T Lymphocytes Regulatory	0.02
MP:0005010	abnormal CD8-positive T cell morphology	2.16E-04	A11.620	Cells	Muscle Cells	Muscle Cells	0.02
MP:0004359	short ulna	3.38E-04	A11.620.520	Cells	Muscle Cells	Myocytes Smooth Muscle	0.02
GO:0001782	B cell homeostasis	3.76E-04	A10.690.467	Tissues	Muscles	Muscle Smooth	0.02
ENSG00000038427	VCAN PPI subnetwork	3.82E-04	A10.165.450.300.425	Tissues	Connective Tissue	Keloid	0.04
MP:0008076	abnormal CD4-positive T cell differentiation	3.91E-04	A02.835.583	Musculoskeletal System	Skeleton	Joints	0.05
MP:0005091	increased double-positive T cell number	6.06E-04	A02.835.583.443.800	Musculoskeletal System	Skeleton	Synovial Membrane	0.05
MP:0004355	short radius	6.22E-04	A02.835.583.443	Musculoskeletal System	Skeleton	Joint Capsule	0.05

III. SUPPLEMENTAL FIGURE LEGENDS.

Supplemental Figure 1. Functional relationships for selected replicated loci in human lung.

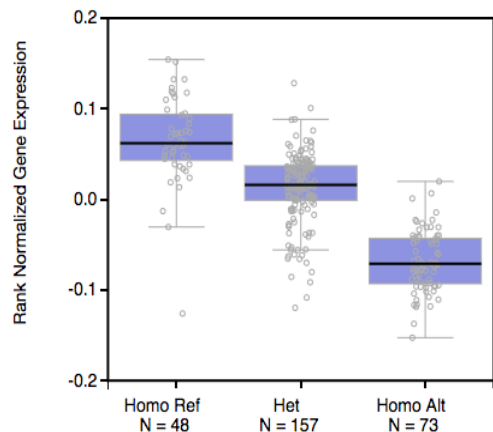
Boxplots were generated for significant eQTLs of interest (rs17843604, rs1420101, rs12998521, rs9272723 and rs9272346), plotted for each sample by genotype, for ENSG00000196735.7 (*HLA-DQA1*) and ENSG00000115602.12 (*IL1RL1*). Circles within boxplots represent expression values for individual samples from lung tissue, present in the GTEX Portal database.

Supplemental Figure 2. Functional roles for replicated 3'UTR variants in *IL1RL1*. The upper plot and boxplots show the localization and effect of *IL1RL1* 3'UTR eQTL SNPs on expression of *IL1RL1* in the lung. The table lists the human miRNA molecules with binding sites on the 3'UTR of *IL1RL1* that are altered by rs12712142.

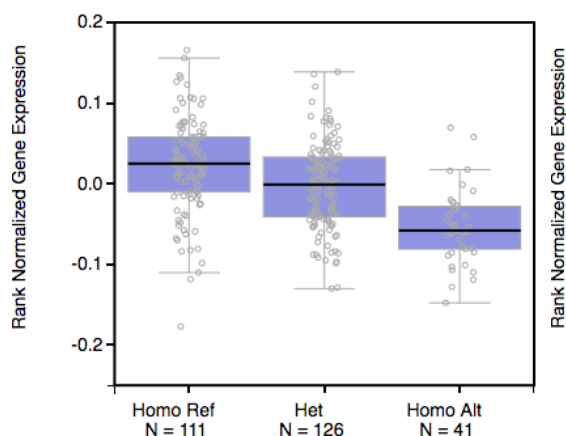
Supplemental Figure 3. Expression of hsa-miR-452-5p in Airway Samples. Barplots show log-normal transformed expression values for hsa-miR-452-5p in (A) airway epithelial cells from asthmatic (N=9) vs. healthy, non-atopic controls (N=7) (GDS3711; GSE18965) and (B) bronchial biopsies from allergic asthmatics vs. healthy normal control samples (N=4) (GDS4418; GSE41659).

Supplemental Figure 4. Plots of regional LD. LocusZoom regional LD plots show the results of conditional SNP analyses for the *HLA-DQA1/HLA-DQB1* region of chromosome 6 (rs17843604) [left panel] and *IL1RL1/IL18R1* region of chromosome 2 (rs1420101) [right panel]. In the top two panels, GERA GWAS results for SNP associations meeting genome-wide significance ($P < 5 \times 10^{-8}$) were first plotted against hg19 1000 genomes reference build for chromosome 6 (pos. 32555182–32661429) [top right panel] and chromosome 2 (pos. 102877961–103018497) [bottom right panel]. Regional LD plots of all GERA GWAS results, after conditioning on either rs17843604 [bottom left panel] or rs1420101 [bottom right panel], are shown for comparison. Symbols in the plots represent individual SNPs, and SNP annotations are indicated by symbol shapes: circle = coding, square = intergenic, diamond = intron, triangle = promoter, inverted triangle = 3'UTR. The top-ranked GWAS SNP is indicated by a purple diamond.

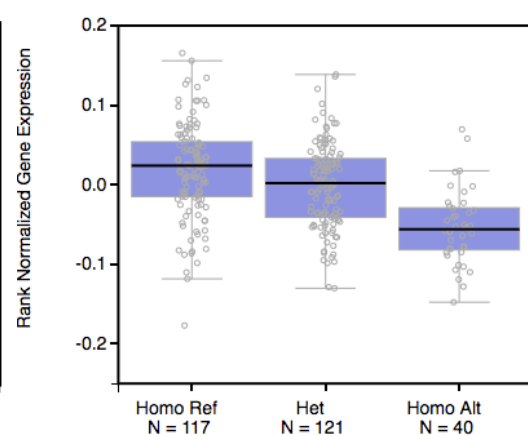
Lung eQTL rs17843604 ENSG00000196735.7



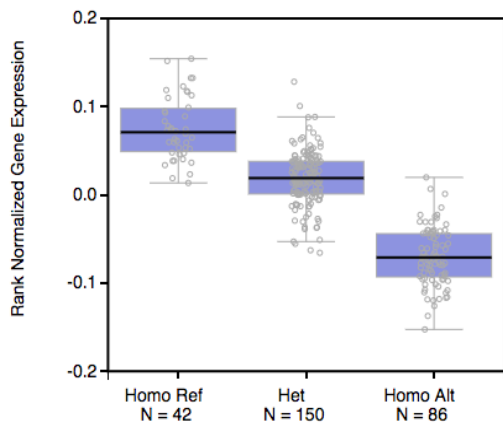
Lung eQTL rs1420101 ENSG00000115602.12



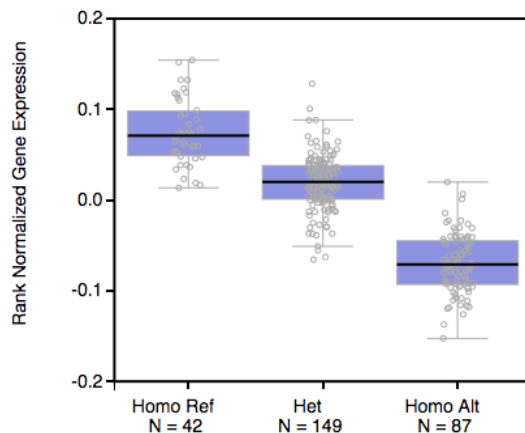
Lung eQTL rs12998521 ENSG00000115602.12

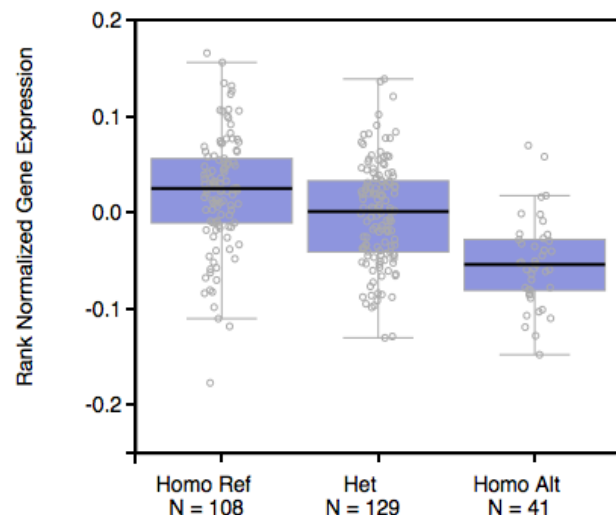
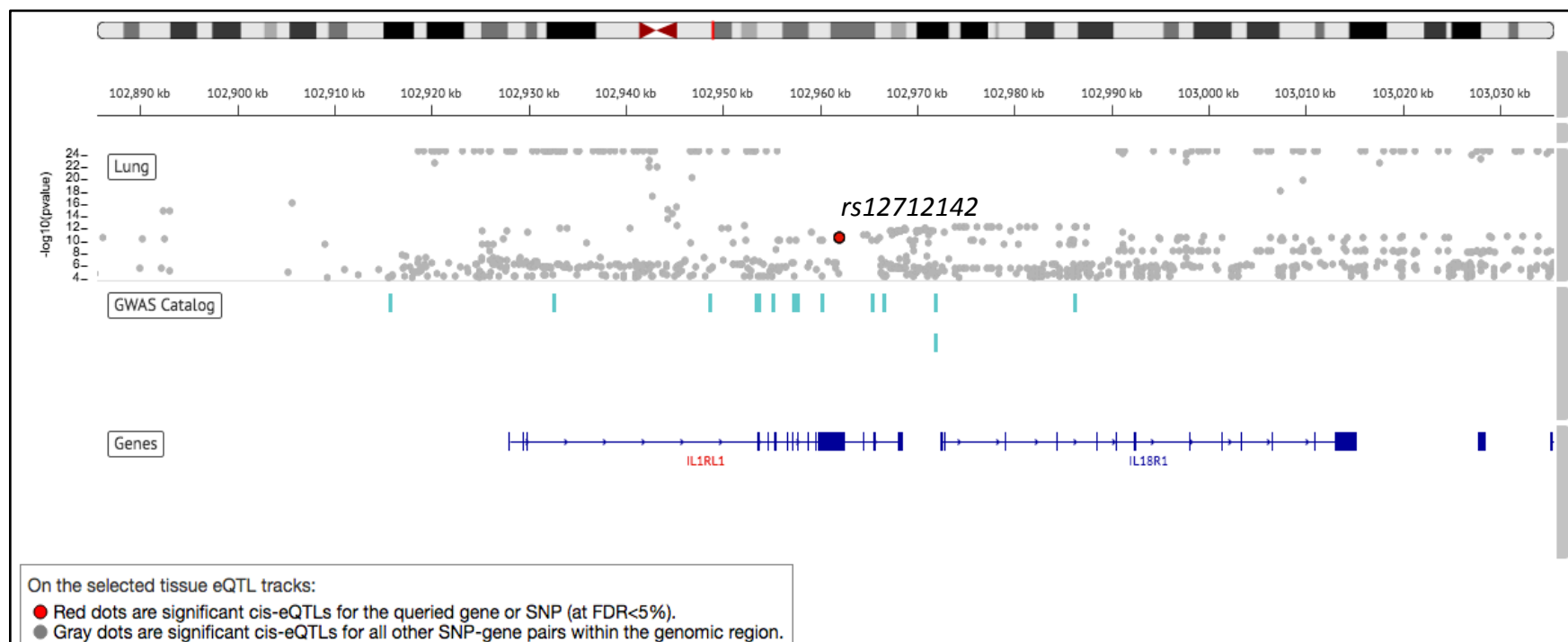


Lung eQTL rs9272723 ENSG00000196735.7



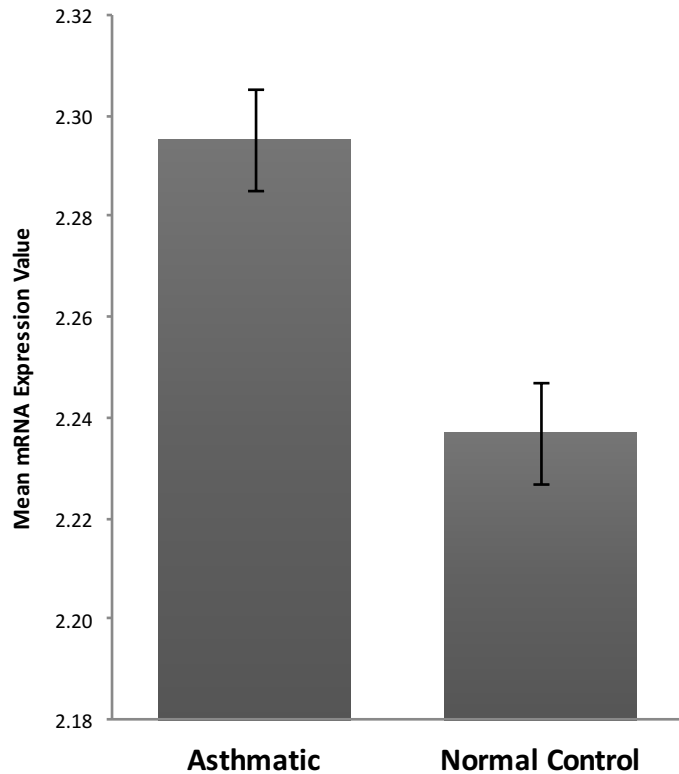
Lung eQTL rs9272346 ENSG00000196735.7



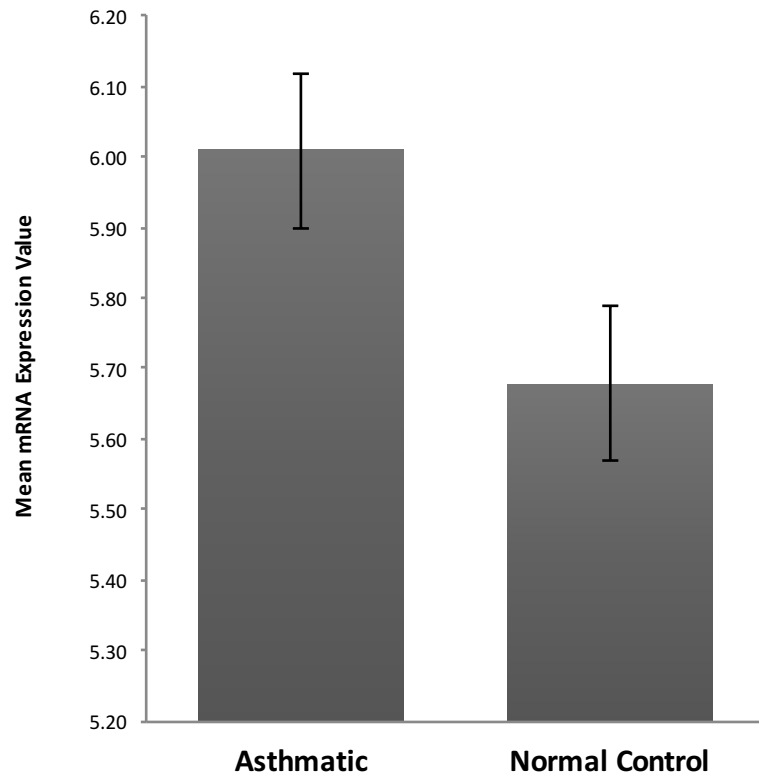


miRNA	Energy change (kcal/mol)	miRNA/SNP-target duplexes	Effect by SNP on 3'UTR Binding Site
hsa-miR-892a	Reference: -20.50 SNP: 0.00	miRNA: 3' gaUGCGUCUUU--CCUGUGUCAc 5' UTR: 5' aaAGGCAGGCACTTCA ^A ACAGTa 3'	Loss
hsa-miR-452-5p	Reference: 0.00 SNP: -19.30	miRNA: 3' caaagGAGACGUUUGUCAa 5' UTR: 5' gcaggCACTTC ^A AACAGTa 3'	Gain
hsa-miR-4676-3p	Reference: 0.00 SNP: -16.90	miRNA: 3' uucUCGGUCACCACUUUGUCAc 5' UTR: 5' ggcAGGCACT--TCA ^A ACAGTa 3'	Gain
hsa-miR-892c-3p	Reference: 0.00 SNP: -17.00	miRNA: 3' aggugagucuuuccUUUGUCAc 5' UTR: 5' aaggcaggcacttc ^A AACAGTa 3'	Gain

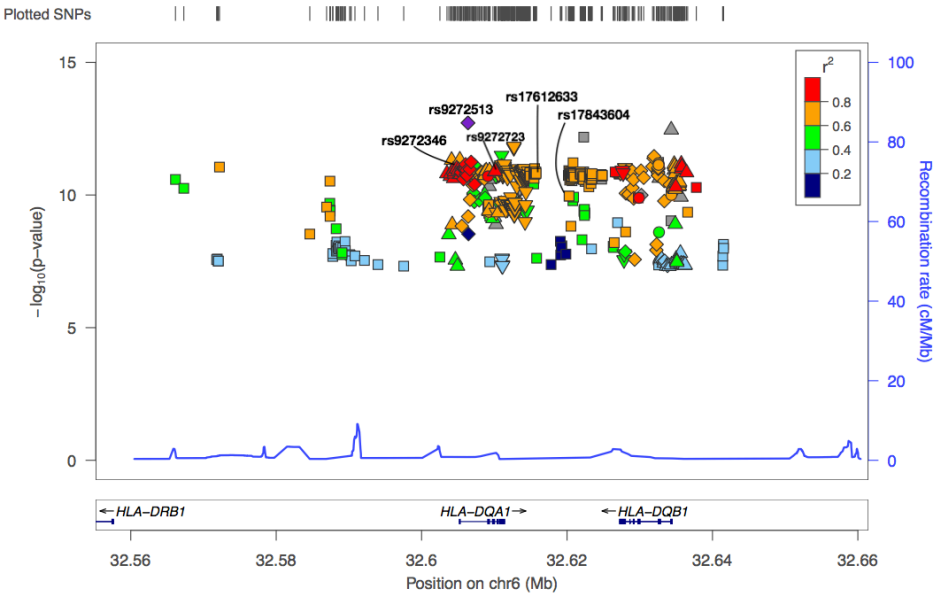
A.



B.



Chromosome 6



Chromosome 2

