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

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Capsule Summary:

In this large, multi-ethnic GWAS of asthma, we identified novel associations with potential functional relevance for asthma susceptibility in older adults of diverse racial backgrounds.

Keywords

asthma; large-scale GWAS; GERA; adult

To the Editor:

Asthma is a genetically heterogeneous disease. While many recent genome-wide association studies (GWAS) have implicated multiple loci associated with asthma risk^{1–4}, the impact of

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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 GWAS 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, trans-ethnic 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 non-asthmatic controls) is provided in Supplemental Table 1. GWASs were conducted for four racial/ethnic groups within GERA (non-Hispanic white, African-American, Asian, and Hispanic), and replicated using data from two large consortia, EVE and GABRIEL. Selected 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, >7 million SNPs passed QC measures and were evaluated by GWAS, of which 646 SNPs met genome-wide significance ($P < 5 \times 10^{-08}$) and were annotated to two regions of chromosomes 2 and 6 that include *IL1RL1/IL18R1* and *HLA-DQA1/HLA-DQB1*, respectively; of these, five SNPs were also genotyped in GABRIEL and four were suggestive in GABRIEL ($P < 1 \times 10^{-05}$) (Fig. 1A; Table 1). Eighteen of the genome-wide significant GERA SNPs were also genotyped in EVE; of these, 14 were nominally significant ($P < 0.05$), and the top two SNPs were suggestive ($P < 1 \times 10^{-05}$) (Table 1). 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. 1A; Table 1). A survey of 32 published asthma GWASs cited in the NHGRI Catalog revealed 113 suggestive associations ($P < 1 \times 10^{-05}$) (Supplemental Table 2). Of these, 87 SNPs (77%) were also genotyped in the GERA non-Hispanic white dataset, 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, 44/87 (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 $P < 5 \times 10^{-08}$ (Supplemental Table 2).

In the three additional racial/ethnic groups in GERA, 6.4–12.7 million SNPs passed QC and were evaluated by GWAS. Three SNPs (rs5756210 downstream of *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. 1A; Supplemental Table 3). 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 four 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 for both *HLA* loci and *IL1RL1/IL18R1* in the lung and circulation (Supplemental Table 4). In addition, rs12712142 was associated with an 11% increased risk of asthma and is an eQTL for *IL1RL1*, reducing transcript expression in the lung (Supplemental Fig. 1). 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 up-regulated in asthmatic airway epithelia compared to samples from healthy, non-atopic controls (Supplemental Fig. 2; Supplemental Fig. 3). Since variations across multiple genes within affected pathways could directly impact asthma phenotypes, we analyzed 2,143 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+, B and T-cell growth, morphology and other activities while seven tissue enrichment sets included pathways for 'T-lymphocytes' and 'CD4 Positive T-lymphocytes' (Supplemental Table 5).

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. Due to differences in GWAS study design, imputation, and available SNP data, the majority of 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 LD between the top discovery GWAS SNPs not genotyped in GABRIEL or EVE and the replicated SNPs shown in Table 1. Conditioning on the lead replicated SNP for chr6, rs17843604, reduced the strength of the regional GWAS association of *HLADQA1* (within 400 kb) to below genome-wide significant levels (top SNP unadjusted P value = 7.5×10^{-07}) (Supplemental Figure 4). Similarly, conditioning on rs1420101 removed all significant associations within 400 kb of the *IL1RL1/IL18R1* region. Finally, while 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 GERA⁷. Nevertheless, like Almoguera et al., 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 four 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 two 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 five unique genes, including *TET2*, which is associated with COPD 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. While 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, while 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 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 multi-ethnic GWAS of asthma to date.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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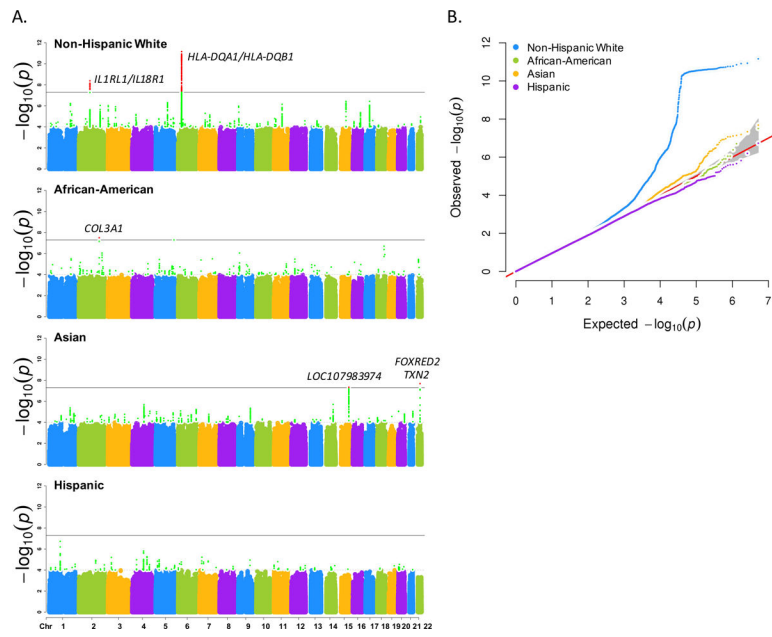


Figure 1. Discovery GWAS Results for GERA Populations.

A. Manhattan plots for each GWAS are provided by racial/ethnic group, with chromosomal positions along the abscissa while $-\log(p\text{-value})$ 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 1.0–1.004.

Table 1.

GWAS Results for Non-Hispanic Whites

SNP	Chr.	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	<i>HLA-DQAI</i>	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	<i>HLA-DQAI</i>	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	<i>ILIRLI</i>	T	1.10 (1.06–1.13)	2.65×10 ⁻⁰⁸	1.11 (1.06–1.15)	9.60×10 ⁻⁰⁷	1.15 (1.0620131.25)	2.87×10 ⁻⁰⁵	8.25×10 ⁻¹⁵
rs12998521	2	102974417	<i>ILIRLI</i>	T	1.10 (1.06–1.13)	1.34×10 ⁻⁰⁸	1.11 (1.07–1.16)	1.39×10 ⁻⁰⁷	1.10 (1.0120131.20)	1.42×10 ⁻⁰³	3.05×10 ⁻¹⁴
rs9272346	6	32604372	<i>HLA-DQAI</i>	G	0.89 (0.97–0.93)	1.13×10 ⁻¹¹	---	---	0.93 (0.8520131.00)	4.29×10 ⁻⁰⁴	1.50×10 ⁻¹²
rs9272723	6	32609427	<i>HLA-DQAI</i>	T	0.89 (0.87–0.93)	2.52×10 ⁻¹¹	---	---	0.92 (0.8520131.00)	1.58×10 ⁻⁰³	4.46×10 ⁻¹²
rs13019081	2	102950822	<i>ILIRLI</i>	C	1.11 (1.07–1.14)	2.09×10 ⁻⁰⁹	---	---	1.11 (1.0220131.22)	3.41×10 ⁻⁰⁴	3.28×10 ⁻¹⁰
rs12712142	2	102960584	<i>ILIRLI</i>	A	1.01 (1.07–1.14)	4.65×10 ⁻⁰⁹	---	---	1.13 (1.0520131.23)	7.15×10 ⁻⁰⁵	5.94×10 ⁻¹⁰
rs13001325	2	102939036	<i>ILIRLI</i>	T	1.11 (1.07–1.14)	3.49×10 ⁻⁰⁹	---	---	1.11 (1.0220131.22)	7.63×10 ⁻⁰⁴	6.43×10 ⁻¹⁰
rs12479210	2	102949161	<i>ILIRLI</i>	T	1.11 (1.07–1.14)	4.32×10 ⁻⁰⁹	---	---	1.11 (1.0220131.22)	3.34×10 ⁻⁰⁴	6.98×10 ⁻¹⁰
rs11123923	2	102967844	<i>ILIRLI</i>	A	1.10 (1.07–1.14)	3.89×10 ⁻⁰⁹	---	---	1.1 (1.0120131.2)	8.32×10 ⁻⁰⁴	7.30×10 ⁻¹⁰
rs950880	2	102932562	<i>ILIRLI</i>	A	1.10 (1.07–1.14)	5.66×10 ⁻⁰⁹	---	---	1.11 (1.0220131.21)	1.88×10 ⁻⁰⁴	8.45×10 ⁻¹⁰
rs6543119	2	102963072	<i>ILIRLI</i>	T	1.10 (1.06–1.13)	7.15×10 ⁻⁰⁹	---	---	1.14 (1.0520131.23)	1.23×10 ⁻⁰⁴	1.01×10 ⁻⁹
rs13017455	2	102964742	<i>ILIRLI</i>	T	1.10 (1.06–1.13)	7.53×10 ⁻⁰⁹	---	---	1.14 (1.0420131.23)	2.50×10 ⁻⁰⁴	1.19×10 ⁻⁹
rs2287037	2	102979028	<i>ILIRLI</i>	T	1.10 (1.06–1.13)	1.14×10 ⁻⁰⁸	---	---	1.10 (1.0220131.22)	6.01×10 ⁻⁰³	3.22×10 ⁻⁹
rs9269080	6	32440969	<i>HLA-DRB9</i>	G	0.91 (0.9–0.95)	2.39×10 ⁻⁰⁸	---	---	0.94 (0.8820131.02)	0.04	1.06×10 ⁻⁸

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.