

HLA-DQ strikes again: Genome-wide association study further confirms HLA-DQ in the diagnosis of asthma among adults

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Summary

Background Asthma is a common chronic respiratory disease in children and adults. An important genetic component to asthma susceptibility has long been recognized, most recently through the identification of several genes (e.g., ORMDL3, PDE4D, HLA-DQ, and TLE4) via genome-wide association studies.

Objective To identify genetic variants associated with asthma affection status using genome-wide association data.

Methods We describe results from a genome-wide association study on asthma performed in 3855 subjects using a panel of 455 089 single nucleotide polymorphisms (SNPs).

Result The genome-wide association study resulted in the prioritization of 33 variants for immediate follow-up in a multi-staged replication effort. Of these, a common polymorphism (rs9272346) localizing to within 1 Kb of HLA-DQA1 (chromosome 6p21.3) was associated with asthma in adults (P -value = 2.2×10^{-8}) with consistent evidence in the more heterogeneous group of adults and children (P -value = 1.0×10^{-4}). Moreover, some genes identified in prior asthma GWAS were nominally associated with asthma in our populations.

Conclusion Overall, our findings further replicate the HLA-DQ region in the pathogenesis of asthma. HLA-DQA1 is the fourth member of the HLA family found to be associated with asthma, in addition to the previously identified HLA-DRA, HLA-DQB1 and HLA-DQA2.

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Introduction

Asthma (MIM 600807) is a syndrome characterized by chronic airway inflammation, airway hyperresponsiveness and intermittent airway obstruction that result in episodic breathlessness, wheeze and cough. Asthma is emblematic of a truly complex disease that develops through the interaction of multiple genetic and environmental factors. The advent of technical and statistical methods for comprehensive genome-wide association studies (GWAS) has helped to identify new loci associated with asthma. The first such study for asthma identified common regulatory variants at and near the *ORMDL3/GSDML* loci on chromosome 17q21 that were associated with asthma in three populations of European ancestry [1]. These associations have been confirmed in many follow-up replications studies, with the *ORMDL3/GSDML* representing one of the most consistent asthma associations reported to date [2–4]. A second asthma GWAS identified common intronic variants in phosphodiesterase 4D (*PDE4D*) to be strongly associated with asthma in Caucasian children and in four of five additional cohorts of diverse ethnicity [5]. A common variant, rs2378383, on chromosome 9q21.31, near transducin-like enhancer of split 4 (*TLE4*), was associated with childhood asthma in two Mexican cohorts, but not in Caucasians [6]. A GWAS study performed in two independent populations of African ancestry identified three variants associated with asthma in both populations: rs10515807, mapping to alpha-1B-adrenergic receptor (*ADRA1B*), rs6052761 near prion-related protein (*PRNP*) and rs1435879 near dipeptidyl peptidase 10 (*DPP10*), although replication for these associations was not observed in either four additional populations of African descent or three populations of European descent [7]. Other recent asthma GWAS identified other potential asthma variants, *RAD50-IL13* [8] and *DENND1B*, on chromosome 1q31.3 [9]. The GABRIEL project, the largest asthma GWAS to date, consisting of 10 365 asthma cases and 16 110 control individuals, identified genome-wide significant associations between asthma and SNPs in or near *IL1RL1/IL18R1*, *IL33*, *SMAD3* and *IL2RB* [10]. The strongest finding was at rs9273349 in the *HLA-DQ* region of chromosome 6p21.3 [10]. Prior to this, the *HLA* region had been identified in several genetic studies as a region associated with asthma and related phenotypes [11–14]. Furthermore, the EVE consortium, a US consortium of similar size to GABRIEL, validated several previously associated regions including loci on 17q21 and genetic variants within the *HLA-DQ* region. In addition, this study identified and replicated several ethnic-specific associations, including a novel association with asthma in the *PYHIN1* gene among subjects of African descent [15].

Although some genetic associations are starting to show consistent, replicable genetic associations, particularly with the larger genetic consortiums, many of the observed genetic associations do not consistently replicate across studies [5, 16–19]. This can be attributed to the heterogeneity of populations studied and differences in statistical power among the studies.

To date, the findings from GWAS have only explained a small percentage of the overall genetic variation for most complex diseases including asthma [20], suggesting that more genetic studies and alternative approaches to gene identification are necessary to localize asthma variants. In addition, the clinical characteristics of asthmatic children and adults are also different; with age, asthmatic symptoms often subside and the nature of the inflammatory response also changes with age. Therefore, the genetic association that is evaluated in children can be described as a causal association with asthma diagnosis, whereas what is evaluated in adults might be described as asthma persistence. It is likely that the genes causing childhood asthma are different from the genes that cause asthma persistence. Additional lines of evidence suggest that the age at onset of asthma may be influenced by genetics, with earlier onset being more likely to implicate a genetic cause for the disease; further suggesting that childhood and adult asthma have important genetic differences [21].

Taken together, it is likely that many additional asthma-susceptibility variants are yet to be discovered. Herein, we describe the results of a GWAS with 3855 subjects, including 1238 asthmatics to further identify and validate genetic variants for asthma.

Methods

Populations

SHARP GWAS cohorts. The SNP Health Association Resource (SHARe) Asthma Resource Project (SHARP) conducted genome-wide genotyping in adults and children who have participated in the National Heart, Lung, and Blood Institute's (NHLBI) clinical research trials on asthma. SHARP includes children with asthma who participated in the Childhood Asthma Management Program (CAMP), children who participated in one or more of five clinical trials conducted by the Childhood Asthma Research and Education (CARE) network and adults who participated in one or more of six clinical trials conducted by the Asthma Clinical Research Network (ACRN). For the purposes of these studies, childhood asthma was defined as meeting the diagnostic criteria for a specific study before the age of 18, whereas adult asthma was defined as meeting the diagnostic criteria for a specific study after the age of 18.

The ascertainment criteria and study designs for each of the studies conducted by these networks were comparable, although not identical. Because both ACRN and CARE are made up of several substudies, we provide the asthma diagnosis criteria for one representative trial from each study. We also provide the diagnosis criteria for CAMP. Additional explicit details of all studies included in SHARP can be found on the dbGaP website (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000166.v2.p1&phv=71260&tphd=1429&tpha=&tpht=700&phvf=&tpdf=&phaf=&tphtf=&tdssp=1&consent=&temp=1). The primary analysis included here was restricted to Caucasian individuals within SHARP.

CAMP. Childhood Asthma Management Program was a multi-centre longitudinal clinical trial that followed 1041 asthmatic children for approximately 4 years with inclusion/exclusion criteria that were developed to select individuals with mild to moderate asthma [22]. CAMP was designed to evaluate whether continuous, long-term treatment (over a period of 4–6 years) with either an inhaled corticosteroid (budesonide) or an inhaled non-corticosteroid drug (nedocromil) safely produces an improvement in lung growth as compared with treatment for symptoms only (with albuterol and, if necessary, prednisone, administered as needed). The primary outcome in the study was lung growth, as assessed by the change in forced expiratory volume in 1 s (FEV₁, expressed as a percentage of the predicted value) after the administration of a bronchodilator. Secondary outcomes included the degree of airway responsiveness, morbidity, physical growth and psychological development. All recruited children had asthma as defined by having two or more symptoms per week, using an inhaled bronchodilator at least twice weekly or asthma medication daily and airway responsiveness to methacholine ≤ 12.5 mg/mL [23]. Children with severe asthma or other clinically significant conditions were excluded. DNA samples from 2241 probands and their parents underwent genome-wide genotyping as described below.

CARE. The Asthma Research and Education Network was established in 1999 by the NHLBI. Five clinical centres and a data co-ordinating centre were selected to participate in this research network. As asthma is the most common chronic childhood disease in the United States, the CARE Network was established to evaluate treatments for children with asthma, conducting studies for children with asthma and sharing their findings with the health care community (<http://www.asthma-carenet.org/index.html>) [24–26]. Asthma diagnosis was similar in all CARE trials. The Pediatric Asthma Controller Trial (PACT) was one of the CARE clinical trials. Asthma diagnosis in PACT was based on the following. First, children had airway responsiveness to methacholine

≤ 12.5 mg/mL. Second, individuals were required to have mild–moderate persistent asthma as defined by either (1) the presence of self-reported symptoms or inhaled bronchodilator (not including pre-exercise) use an average of at least four times per week during the 4 weeks preceding the trial or (2) the presence of diary-reported symptoms or inhaled bronchodilator (not including pre-exercise) use or peak flows in the yellow zone an average of at least four times per week during the 2-week run-in to the clinical trial. DNA samples from 1604 probands and their parents underwent genome-wide genotyping.

ACRN. Asthma Clinical Research Network was established in 1993 by the NHLBI. The objectives of this multi-centre program are to conduct multiple well-designed clinical trials for rapid evaluation of new and existing therapeutic approaches to asthma and to disseminate laboratory and clinical findings to the health care community. From 1993 to 2003, ACRN consisted of six clinical centres and one data co-ordinating centre [26, 27]. Asthma diagnosis was similar in all ACRN trials. In general, the diagnostic criteria for asthma included history of physician diagnosis of asthma and tests for reversible airflow obstruction and/or bronchial hyperresponsiveness. Here, we describe the diagnosis criteria for one representative study, IMProving Asthma Control Trial (IMPACT). Asthma diagnosis was defined in IMPACT by 1) a history of asthma and 2) heightened airway reactivity, shown by reversible airflow obstruction $\geq 12\%$ and ≥ 200 mL improvement in FEV₁ following two to four inhalations of albuterol MDI or by methacholine PC20 ≤ 8 mg/mL. DNA samples from 1059 individuals underwent genome-wide genotyping as described below.

Population controls. We obtained data corresponding to 1432 control individuals from a GWAS of schizophrenia and bipolar disorder [28] that was submitted to dbGaP [<http://www.ncbi.nlm.nih.gov/gap>]. These individuals did not have a diagnosis of schizophrenia or bipolar disorder and they were not ascertained for the presence or absence of asthma. Therefore, these individuals are considered ‘population controls’ and can be reasonably assumed to have asthma at the rate that is prevalent in the general population.

Genotyping and quality control measures

Affymetrix, Inc. (Santa Clara, CA, USA) performed the genotyping according to manufacturer’s protocol using the Affymetrix Genome-Wide Human SNP Array 6.0. Marker quality control (QC) was performed on all autosomal markers, which were extracted from dbGAP for each of the four cohorts. SNPs were excluded for the following reasons: (1) probe sequence did not map

uniquely to the hg18 genome build; (2) genotyping completion rate < 95%; (3) P -value for Hardy–Weinberg equilibrium (HWE) $\leq 1\text{E-}06$; and (4) > 12 discordances observed among sample replicate pairs. We excluded all SNPs with Mendelian error counts ≥ 4 in either CARE or CAMP trios. Genotypic gender was verified in PLINK [29]. Subject relatedness was verified using rgGRR [30], and by confirming very low rates of parent–child genotype inconsistencies (average within-family rate of 0.14%). Specific information on the QC procedures for individual datasets is available in the Supplemental Data. The data were adjusted for population stratification using Eigenstrat [31] (see Appendix S1).

Statistical analysis

Three primary GWAS analyses were performed: (1) an analysis of all adult asthmatics; (2) an analysis of all childhood asthmatics; and (3) an analysis of the childhood and adult asthmatics combined. We maximized the use of the data by employing both regression-based techniques for case-control data and family-based association tests for family data. Details of the analysis can be found in the Appendix S1.

SNPs were selected for replication using the following approach: First, we verified that the direction of the observed effect was consistent across our primary analyses in children (i.e. CAMP, CARE and Genetic Association Information Network, GAIN), adults (i.e. ACRN and GAIN) and all subjects (i.e. CAMP, CARE, ACRN and GAIN). Second, we identified the SNPs with P -values < $1\text{E-}04$ from the combined analysis of all subjects. When replication SNPs were not available in replication populations due to differences in genotyping platforms, we identified and evaluated the associations at SNPs that were either in strong linkage disequilibrium with the identified SNP or analysed the imputed SNP data. Joint evidence for association across populations was measured by combining P -values using the sample size-weighted Liptak method [32]. In combining P -values, hypothesis tests in replication populations had one-sided alternatives (based on the direction of association in the primary SHARP analysis) so that SNPs with association tests in opposite directions would not produce inappropriately small P -values. Overall statistical significance was determined after adjusting for the total number of statistical tests performed based on the total number of genotyped SNPs.

Replication populations

Replication analyses were performed in five cohorts: (1) Children's Hospital of Philadelphia (CHOP); (2) Children's Health Study (CHS); (3) Costa Rica; (4) Sepracor/LOCCS/LODO/Illumina; and (5) i2b2 Crimson Asthma

Project (iCAP). Details about these cohorts are included in Appendix S1. Each replication study was approved by the Institutional Review Board of the corresponding institution and informed consent was obtained for all study participants.

Results

We performed a GWAS of asthma, combining the three well-characterized asthma cohorts from SHARP and dbGaP population controls genotyped using the Affymetrix 6.0 SNP array. Following exclusion of individuals and markers that did not meet stringent QC criteria, the final dataset consisted of 3855 subjects and 455 089 markers (Tables 1 and 2). In addition to analysing all asthma subjects, we performed separate analyses of childhood and adult asthma. The sample size of

Table 1. Primary population characteristics

	CAMP	CARE	ACRN	GAIN
Ascertainment method	Clinical trial	Clinical trials	Clinical trials	GWAS control cohort
Number of total individuals	1280	756	471	1348
Number of probands/cases	556	211	471	0
Number of parents/controls	724	545	0	1348
Age (SD) [min, max]	8.8 (2.14) [5.2,13.2]	10.6 (3.45) [2.2,17.8]	32.5 (10.8) [12.4,65.2]	50.9 (17.0) [18,90]

ACRN, Asthma Clinical Research Network; CAMP, Childhood Asthma Management Program; CARE, Childhood Asthma Research and Education.

Table 2. Summary of the three primary GWA designs

	Childhood asthmatics	Adult asthmatics	Combined analysis
Total sample size	3442	1819	3855
Number of cases/probands	767	471	1238
Number of controls	1348	1348	1348
Number of parents	1269	0	1269
Analysis method	New screening method	Logistic regression	New screening method
Power estimate*	0.86	0.64	0.98

*This estimate corresponds to the power to detect that a SNP will be among the top 40 SNPs of the GWAS, assuming an OR = 1.5, a MAF = 0.2, and a disease prevalence of 0.10. The adult analysis had the lowest statistical power. The childhood and combined analyses had adequate statistical power.

the childhood analysis is nearly double that of the adult analysis, both with respect to number of probands/cases and number of total subjects, leading to greater power (~22% more) to detect genetic association in the childhood asthma analysis than in the analysis of adult cohorts (Table 2).

Quantile–quantile plots for all three GWA analyses indicate that the top association P -values are slightly lower than what is expected by chance for the children's and combined GWAS analysis, in keeping with the conservative nature of the test statistics employed (Figure S1). Despite the conservative nature of the results, the top association P -values obtained via our method are the best candidates for future replication of a study because the analysis methodology maximizes statistical power by combining case-control and family-based data [33]. Deviation from the null distribution was observed among the lowest P -values in the adult analysis, suggesting enrichment for significant associations, with two SNPs (rs17441370 and rs272474) meeting genome-wide significance. SNP rs17441370 resides on chromosome 14q13.1 within an intronic region of *AKAP6*. SNP rs272474 resides on chromosome 5p15.31 within an intronic region of ubiquitin-conjugating enzyme E2Q family-like 1 *UBE2QL1*. However, both these SNPs had MAFs just above 5% and our statistical power is limited to rigorously assessing these associations due to the relatively small sample size of the adult cohort. Therefore, these SNPs were not included in the immediate replication efforts. The other top association P -values for the

childhood, adult and combined analysis are in the range of $1\text{E-}07$ and $1\text{E-}06$, and do not reach statistical significance after correcting for multiple comparisons (Fig. 1). Detailed lists of the top (i.e. $< 1\text{E-}04$) association P -values for each of the primary analyses are included in the Appendix S1 (Tables S1, S2 and S3).

The top 33 SNPs (i.e., P -value $< 1\text{E-}04$) (Table S3) from the combined analysis with consistent effect estimates across the childhood and adult cohorts were selected for replication in four independent populations (CHS, CHOP, Costa Rica, Sepracor/LOCCS/LODO/Illumina). Of the 33 SNPs, we obtained association data in at least one population for 19 SNPs, or SNPs in strong LD to the initial SNP. After taking consistency of effect direction into account, two (i.e. rs9272346, rs1121336) of the 19 SNPs had nominally significant P -values in at least two populations (i.e. the P -value is less than 0.05 before multiple comparison correction) (Table 3). SNP rs9272346 in *HLA-DQA1* (6p21.3) achieved genome-wide significance in the adult cohort where the initial P -value was $1.2\text{E-}07$ and the final combined P -value was $2.2\text{E-}08$ after including two adult replication cohorts (Sepracor/LOCCS/LODO/Illumina P -value = 0.032 and iCAP P -value = 0.042). Further details on this SNP are provided in Table 3, where the association P -values are listed for the childhood, adult and combined cohorts. Although this effect was the strongest in the adult cohort, there is evidence that this association may also exist in children (and hence the combined analysis as well), as the initial P -value was nominally

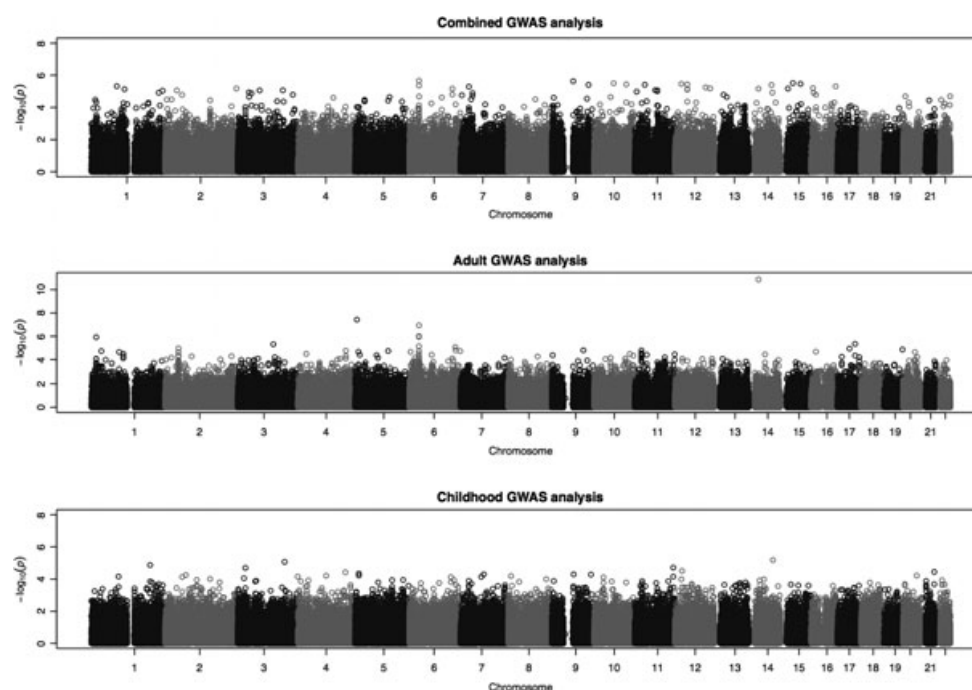


Fig. 1. Manhattan plots of the three GWA analyses: 1) All asthmatics; 2) Adult asthmatics; 3) Childhood asthmatics. The x-axis represents the chromosomal position of the association test that took place for each SNP. The y-axis represents the $-\text{Log}_{10}(\text{p-value})$ of the association test.

Table 3. Results for the SNP with strongest evidence of replication across all cohorts

SNP	MA	SHARP		Study Type	CHS	Costa Rica (children)	Sepracor/ LOCCS/ LODO/ Illumina		iCAP (adult)	Gene	Overall Replication P-value	Combined P-value including SHARP Result	
		Analysis P-value	P-value/OR				CHOP (children)	P-value/OR					P-value/OR
rs9272346	G	5.9E-05	0.0019/0.76*	0.48/1.00	Combined	0.83/1.04 [†]	0.039/0.85	0.032/†	0.042/0.93	HLA-DQA1	0.027	1.0E-04	
		5.0E-03	0.0019/0.76*	0.48/1.00	Childhood	0.83/1.04 [†]	0.039/0.85	N/A	N/A	N/A	0.075	4.8E-03	
		1.16E-07	N/A	N/A	Adult	N/A	N/A	0.032/†	0.042/0.93		0.0067	2.2E-08	

*CHS association data for this SNP is based on imputed data and is thus divided into two P-values. Top result corresponds to Hispanic White subjects; bottom result corresponds to Non-Hispanic White subjects. The combined P-values treat the two results as corresponding to two populations of the corresponding size.

†Association values for CHOP are for rs1063355 (MA=A), which is in strong LD ($r^2 = 0.97$) with rs9272346.

MA, minor allele; OR, odds ratio.

P-values in replication populations are 1-sided to take differences of effect direction in replication populations relative to primary SHARP analysis into account.

significant (P -value = 0.0053) and the association finding was replicated in CHS Hispanic white subjects (P -value = 0.0019) and the Costa Rica (P -value = 0.039) cohort.

We compared our results to previously published asthma GWAS (Table 4). Of 14 loci representative of previously reported association from asthma GWAS, adequate SNP tagging ($r^2 \geq 0.80$) by a SNP tested in our study was available for eight SNPs. Nominal association ($P < 0.05$) was observed for four of the eight SNPs: rs1420101 at the *IL1RL1/IL18R1* locus (P -value = 0.01); rs1763231444 tagging rs2416257 at the *TSLP/WDR* locus (P -value = 0.001); rs992969 tagging rs3939286 at the *IL33* locus (P -value = 0.005); and rs4795403 tagging rs7216389 at the *ORMDL3/GSDML* locus (P -value = 0.039). For these associations, statistical significance is achieved for previously associated SNPs at an alpha level of 0.05 because we are evaluating previously identified genetic associations at individual SNPs. Despite being nominally associated with asthma in our study, none of these variants ranked among the most significant ones.

Discussion

We performed a large GWAS of asthma and identified several novel asthma candidates that demonstrated strong association in both children and adults. Of these, SNP rs9272346, near *HLA-DQA1*, achieved genome-wide significance in the adult population. The association finding was also observed in some, but not all, childhood cohorts. The *HLA-DQA1* locus is among the MHC class II loci frequently associated with asthma and allergic phenotypes in diverse populations [12, 14, 34–39]. In addition to *HLA-DQA1*, the *HLA-DR/DQ* region on chromosome 6p21.3 has also been associated with asthma in several previous GWAS. Specifically, rs9273349 was found to have a genome-wide significant association with asthma in a case-control study with over 10 000 physician-diagnosed asthmatics and over 16 000 controls. An evaluation of the HapMap data suggests that rs9272346 and rs9273349 are in linkage disequilibrium with each other. Therefore, rs9272346 is not likely an independent marker for asthma, but represents the same region that was identified and replicated previously using rs9273349, suggesting that our findings further replicate this *HLA-DQ* region.

The HLA region of the genome is highly polymorphic, containing over 224 genes that are associated with over 100 different autoimmune and infectious diseases [40]. The literature on HLA and asthma goes back at least 20 years with over 500 articles described in pubmed. In the genomic era, the first HLA gene described to be associated with asthma was *HLA-G* [41]. Although this study does not identify any polymorphisms within *HLA-*

Table 4. SHARP analysis association *P*-values for previously reported associations in asthma GWAS studies in SNP and tagging SNP

Position	Nearby gene(s)	SNP	Original <i>P</i> -value	Population	Reference	SHARP <i>P</i> -value
2q12	<i>IL1RL1/IL18R1</i>	rs1420101	6×10^{-12}	Caucasian, East Asian	[43]	0.01
2q12	<i>IL18R1</i>	rs3771166	4×10^{-12}	Caucasian	[10]	0.002
2q12.3	<i>DPP10</i>	rs1435879	3×10^{-6}	African ancestry	[7]	0.32
5q12	<i>PDE4D</i>	rs1588265	4×10^{-7}	Caucasian	[5]	0.07
5q22	<i>WDR/TSRP</i>	rs2416257	1×10^{-4}	Caucasian, East Asian	[43]	0.001
5q31.1	<i>RAD50-IL13</i>	rs2244012	3×10^{-7}	Caucasian	[8]	0.40
6p21	<i>HLD-DQ</i>	rs9273349	7×10^{-14}	Caucasian	[10]	0.05
9q21.31	<i>TLE4</i>	rs2378383	7×10^{-7}	Hispanic / Mexican	[6]	0.74
9q24	<i>IL33</i>	rs3939286	5×10^{-6}	Caucasian, East Asian	[43]	0.005
9q24	<i>IL33</i>	rs1342326	9×10^{-12}	Caucasian	[10]	0.09
15q22	<i>SMAD3</i>	rs744910	4×10^{-9}	Caucasian	[10]	0.72
17q21	<i>ORMDL3/GSDML</i>	rs7216389	9×10^{-11}	Caucasian	[1]	0.04
17q21	<i>GSDMB</i>	rs2305480	6×10^{-23}	Caucasian (children)	[10]	0.14
17q21	<i>GSDMA</i>	rs3894194	3×10^{-17}	Caucasian (children)	[10]	0.07
20q12	<i>PRNP</i>	rs6052761	2×10^{-6}	African ancestry	[7]	0.65
22q13	<i>IL2RB</i>	rs2284033	1×10^{-8}	Caucasian	[10]	0.51

*rs2786098, rs275358, rs10515807, rs1063355, rs9494145, rs1358786, rs1326772 were also reported in the literature; however there were no adequate tagging SNP in this study to replicate these findings.

G, the large number of associations within the HLA region suggests that there are likely multiple genetic variants within this region that influence asthma susceptibility. Recently, investigators have identified the DR/DQ region that has now been replicated in four separate studies [42, 43]. Strong links between HLA and both *IL4* and *TNF* alpha, two of the most replicated candidate genes, emphasize the relationship of HLA to Th2 inflammatory responses. The model suspected for autoimmune disorders is one of HLA specificity and interaction with an environmental antigen simulating an infectious pathogen, either viral or bacterial, via molecular mimicry. In the case of asthma, there appears to be less HLA specificity than is seen in inflammatory bowel disease and celiac disease. Nonetheless, the HLA association results suggest that Th1 (IBD and Celiac Disease) and Th2 (Asthma) autoimmune diseases may be more similar than previously thought.

We evaluated the association of several previously identified associations with asthma and observed significant associations ($\alpha = 0.05$) in half of these SNPs. We note that SNPs near *ORMDL3/GSDML*, the most consistent and widely replicated region associated with asthma, replicates in our SHARP sample. Although SHARP results support half of previously identified asthma GWAS top hits that were tested, the lack of replication of remaining top hits may be due to: (1) genetic heterogeneity among GWAS populations; (2) insufficient statistical power in SHARP to identify small genetic effects; or (3) age-dependent genetic effects.

When performing genetic analyses of phenotypes such as asthma, it is important to consider that age-dependent genetic effects may influence the asthma

phenotype differently for children and adults [44]. This hypothesis is quite intuitive, as asthmatic children have distinctly different clinical characteristics than asthmatic adults. In addition, adult asthmatics may represent a more severe group of individuals, as many of the milder asthmatic cases resolve by adulthood. In this analysis, we evaluated both the stratified and combined genetic analyses of asthma based on age in an effort to consider the time-dependent nature of asthma. We found that the rs9273349 association finding is notably stronger in the adult asthma cohorts compared to the childhood cohorts. Although the effect of rs9273349 is not completely absent in the childhood cohorts, this association would not have been identified had the childhood cohorts only been evaluated. This suggests that either the childhood cohorts by themselves are underpowered or that age-dependent genetic effects exist for asthma. We selected SNPs for replication based on the combined genetic analysis results to maximize statistical power by utilizing the maximum sample size possible. Further research should be conducted to scrutinize the potential age-dependent genetic effects both in the childhood and adult asthmatic samples by selecting replication SNPs for each sample individually.

The SHARP population is complex because it is made up of several clinical trials. While CAMP is one large trial, CARE and ACRN are comprised of multiple clinical trials. As such, the ascertainment criteria vary throughout SHARP. Some include adults (ACRN) while others include children (CAMP, CARE). Although inclusion criteria varies among the SHARP studies, doctor's diagnosis of asthma, which is considered the gold standard for asthma diagnosis, is the minimum criterion

used. Therefore, although the various clinical trials included in SHARP are heterogeneous in nature, the gold standard for asthma diagnosis is consistently used at a minimum for asthma diagnosis. It is also important to consider how the incorporation of control individuals from the general population affect the analysis results. The control individuals we selected will have asthma at the rate that is observed in the general population (roughly 5%), which will lead to misclassification and hence decreases the overall power of our analysis. The initial manuscript that discusses the analytic method proposed here, evaluated the effect of using unselected controls on the overall power of the analysis and although this reduces the overall power of the analysis, it does not bias the results [33].

In summary, this GWAS identifies a novel sequence variant that is primarily associated with asthma in adults, although there is evidence to suggest that this association also exists among children. Together with the loci described in prior asthma GWAS and with previously validated candidate genes, the common genetic variation underlying asthma is gradually being elucidated.

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The following authors contributed to the data analysis for this grant: Lasky-Su, Himes, Lange.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Quantile-quantile plot comparing the GWAS analysis p-values to those expected under the null hypothesis. Deviations of measures in the tails indicate that both the Childhood analysis and the combined analysis are conservative. This is not surprising, given that the methodology is slightly conservative; however, the top association p-values remain the most promising for further replication. The adult analysis demonstrates deviations in this tail that may indicate true associations with asthma.

Appendix S1. Individual study detail on genotyping and data cleaning.

Appendix S2. Complete rosters of the members of the SHARP networks.

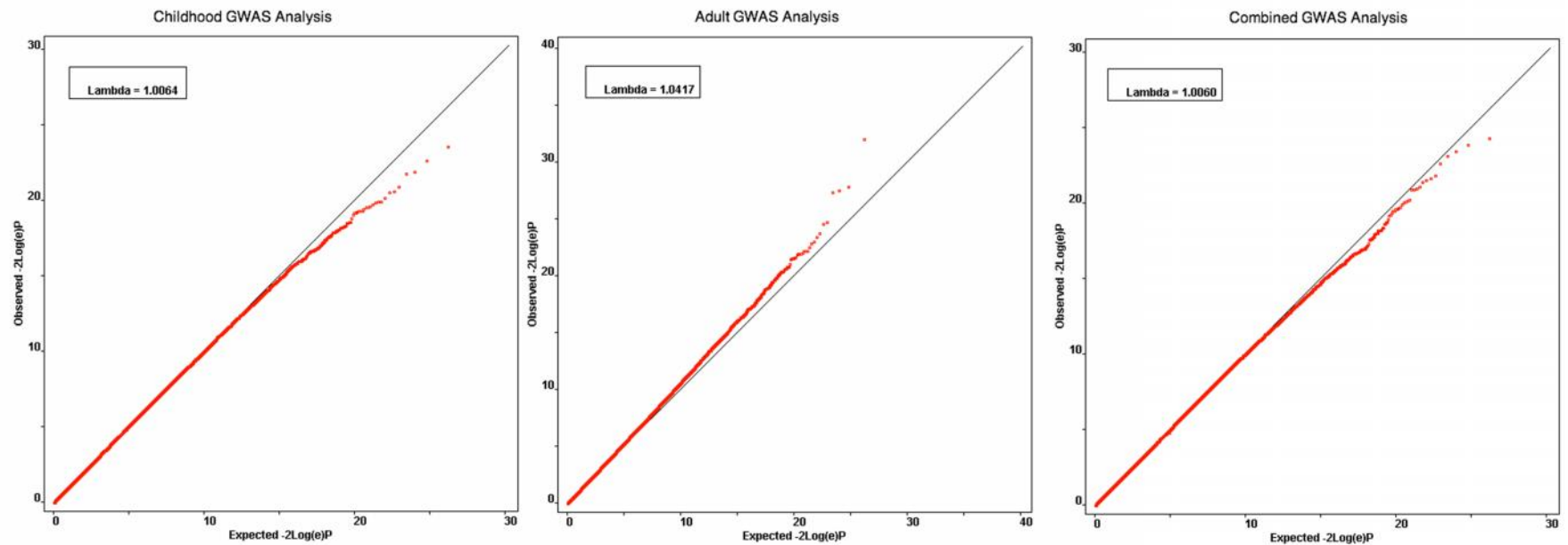
Table S1. Lists the lowest association *P*-values for the analysis of asthmatic children. None of these findings meet genome-wide significance.

Table S2. Lists the top association *P*-value with the adult asthmatic group.

Table S3. Shows the top association *P*-values from the combined analysis of children and adult asthmatics.

Figures

Supplemental Figure 1. Quantile-quantile plot comparing the GWAS analysis p-values to those expected under the null hypothesis. Deviations of measures in the tails indicate that both the Childhood analysis and the combined analysis are conservative. This is not surprising, given that the methodology is slightly conservative; however, the top association p-values remain the most promising for further replication. The adult analysis demonstrates deviations in this tail that may indicate true associations with asthma.



AppendixS1. Individual study detail on genotyping and data cleaning.

Table S1. lists the lowest association p-values for the analysis of asthmatic children. None of these findings meet genome-wide significance.

Table 1S: Top association p-values from the Children's GWAS analysis using the new screening method					
SNP	allele	Chromosome	BP	p-value	Genes(s)
rs179260	T	14	80511808	6.55E-06	<i>TSHR</i>
rs12493149	T	3	155859208	8.46E-06	
rs1322916	C	1	197142881	1.35E-05	
rs1940108	T	11	129155661	1.94E-05	
rs13072262	A	3	25106574	2.01E-05	
rs9804956	T	12	23873055	3.12E-05	<i>SOX5</i>
rs8132754	T	21	41953780	3.61E-05	
rs9991982	T	4	159001480	3.80E-05	
rs4558991	G	5	12752253	4.49E-05	
rs11770702	G	7	78087103	5.08E-05	<i>MAGI2</i>
rs11787887	T	9	72681299	5.10E-05	<i>TRPM3</i>
rs2240956	C	9	130088581	5.25E-05	
rs1106518	A	2	69181722	5.67E-05	<i>ANTXR1</i>
rs7721328	C	5	12705832	5.99E-05	
rs226839	T	20	46309944	6.09E-05	
rs7699958	G	4	94972902	6.24E-05	<i>ATOH1</i>
rs10503404	G	8	10122769	6.46E-05	<i>MSRA</i>
rs1887054	G	1	91872329	6.93E-05	<i>TGFRB3</i>
rs17745701	G	4	106981	7.00E-05	<i>ZNF718</i>
rs10791048	C	11	129162426	7.03E-05	<i>TMEM45B</i>
rs3094893	G	7	69608956	7.24E-05	<i>AUTS2</i>
rs2111724	T	2	56945042	7.38E-05	
rs1212985	G	6	139269223	7.42E-05	<i>REPS1</i>
rs7894459	T	10	31651262	7.83E-05	<i>TCF8</i>
rs4241546	A	3	20122566	8.98E-05	<i>PCAF</i>
rs7578361	G	2	150105464	9.89E-05	
rs10101575	C	8	127412874	0.00010124	
rs11046127	T	12	21622789	0.000102153	<i>GYS2</i>
rs2984272	T	14	50262963	0.000104511	<i>NIN</i>
rs6726692	G	2	105527038	0.000112317	

Table S2. lists the top association p-value with the adult asthmatic group.

Table 2S: Top association p-values for Adult asthmatic analysis					
SNP	allele	Chromosome	BP	p-value	Gene(s)
rs17441370	T	14	32314865	1.369E-11	<i>AKAP6</i>
rs272474	A	5	6515338	3.782E-08	<i>FLJ25076</i>
rs9272346	G	6	32712350	1.161E-07	<i>HLA-DQA1</i>
rs9268853	C	6	32537621	9.550E-07	
rs9268858	C	6	32537736	1.134E-06	
rs2235927	A	1	17267362	1.208E-06	<i>PADI2</i>
rs4343	A	17	58919763	4.504E-06	<i>ACE</i>
rs12634401	C	3	118273713	4.786E-06	
rs9268831	T	6	32535726	7.231E-06	
rs2171249	C	6	153735722	8.450E-06	
rs6706053	T	2	44371166	1.067E-05	<i>SLC3A1</i>
rs17546822	C	17	40364496	1.125E-05	
rs12977381	A	19	62676002	1.359E-05	<i>DKFZp686I1569</i>
rs10820351	T	9	104837653	1.562E-05	
rs7739184	G	6	154670546	1.574E-05	<i>PIP3-E</i>
rs17306398	C	11	23148811	1.619E-05	
rs11723634	C	4	160486784	1.698E-05	
rs6594499	A	5	110498036	1.803E-05	<i>WDR36</i>
rs9268403	C	6	32449451	1.816E-05	<i>C6orf10</i>
rs4653032	A	1	34675497	1.819E-05	
rs7740799	T	6	169730597	1.855E-05	<i>WDR27</i>

rs11075345	T	16	17264958	2.091E-05	<i>XYLT1</i>
rs4702810	T	5	11571226	2.122E-05	<i>CTNND2</i>
rs4144547	T	6	4860422	2.165E-05	<i>CDYL</i>
rs12481621	A	20	39943319	2.204E-05	
rs236313	C	1	93862296	2.244E-05	<i>BCAR3</i>
rs3768919	G	2	44366475	2.285E-05	<i>SLC3A1</i>
rs16910754	T	11	23148591	2.773E-05	
rs4604720	A	1	107638682	3.151E-05	<i>NTNG1</i>

Table S3. shows the top association p-values from the combined analysis of children and adult asthmatics.

Table 3S: The top association findings for adult and pediatric asthma samples combined					
SNPs	Allele	MAF	Chromosome	p-value	Gene
rs4765045	G	0.12	12	2.06E-06	<i>TMEM132B</i>
rs12533496	T	0.13	7	5.76E-06	
rs7927997	T	0.41	11	7.21E-06	<i>Chr11orf30, LRRC32 = GARP</i>
rs7927894	T	0.41	11	8.81E-06	<i>Chr11orf30, LRRC32</i>
rs12826619	C	0.44	12	1.05E-05	
rs2853288	A	0.13	8	1.33E-05	
rs179260	T	0.09	14	1.97E-05	<i>TSHR,TSHR</i>
rs1945486	T	0.06	18	2.19E-05	
rs4558991	G	0.19	5	2.31E-05	<i>AY330599</i>
rs13025711	C	0.34	2	2.47E-05	<i>AK125001</i>
rs12599188	C	0.12	16	2.83E-05	<i>HS3ST2</i>
rs12493149	T	0.26	3	3.03E-05	
rs11704523	A	0.126	22	3.10E-05	<i>LIMK2,LIMK2,LIMK2,MGC17330</i>
rs11075345	T	0.14	16	3.11E-05	<i>XYLT1</i>
rs11770702	G	0.07	7	4.43E-05	<i>MAGI2</i>
rs226839	T	0.07	20	4.49E-05	
rs7721328	C	0.19	5	4.66E-05	
rs9991982	T	0.43	4	4.77E-05	
rs340900	T	0.44	9	5.14E-	<i>IL33, RANBP6</i>

				05	
rs1144219	T	0.37	11	5.57E-05	<i>GLB1L3</i>
rs1121336	C	0.24	4	5.76E-05	<i>ADAM29</i>
rs9272346	G	0.39	6	5.88E-05	<i>HLA-DQA1</i>
rs4862585	T	0.44	4	5.90E-05	<i>SORBS2</i>
rs6726692	G	0.42	2	6.33E-05	
rs1940108	T	0.18	11	6.42E-05	
rs17682661	2	0.31	5	6.69E-05	<i>AGGF1</i>
rs1476458	3	0.13	16	7.12E-05	
rs7894459	4	0.07	10	7.33E-05	<i>TCF8</i>
rs279880	1	0.40	9	8.28E-05	<i>DMRT3</i>
rs11616866	1	0.32	13	9.19E-05	
rs2984272	4	0.29	14	9.30E-05	<i>NIN</i>
rs1702585	3	0.28	11	9.70E-05	
rs765302	3	0.47	20	9.87E-05	
rs11991146	2	0.26	8	0.0001098	<i>CSMD1</i>
rs7130588	3	0.38	11	0.0001099	<i>C11orf30</i>
rs2240449	1	0.18	7	0.0001152	<i>THAP5, DNAJB9</i>
rs16949218	1	0.15	18	0.0001200	<i>ZBTB7C</i>
rs1526413	1	0.20	7	0.0001202	
rs576778	4	0.07	8	0.0001206	
rs7792246	2	0.30	7	0.0001206	<i>SEPT7</i>
rs2223753	4	0.47	20	0.0001302	

SHARP Executive Committee Roster**March 2008**

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Protocol Review Committee: Gary W. Hunninghake, MD (Chair), Iowa City, IA; Robert O. Crapo, MD, Salt Lake City, UT; Richard Nicklas, MD, Washington, DC; Robert C. Strunk, MD, St. Louis, MO; John E. Connett, PhD, Minneapolis, MI; Malcom R. Sears, MD, Hamilton, Ontario, Canada; Donald P. Tashkin, Los Angeles, CA.

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Pharmaceutical Suppliers:

Proventil, active and placebo – Schering Corporation.

Equipment Support:

Computer monitor, central processing unit, keyboard – S&M Instrument Company; Stadiometers – Seritex, Inc.; MiniWright Peak Flow Meters – MiniWright; Chronolog Devices – Meditrac Technologies.

DICE: Dose of Inhaled Corticosteroids with Equisystemic Effects

Supported by: Grants U10 HL 51831, U10 HL 51834, U10 HL 51843, U10 HL 51810, U10 HL 51823, U10 HL 51845, and U10 HL 56443 from the National Heart, Lung, and Blood Institute.

The members of the ACRN for DICE trial included:

Clinical Centers:

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Pharmaceutical Suppliers:

Ventolin, active and placebo – Glaxo Wellcome Inc.; Vanceril, active and placebo – Schering Corp.; Pulmicort, active and placebo – Astra USA; Aerobid, active and placebo – Forest Pharmaceuticals Inc.; Flovent, active and placebo – Glaxo Wellcome Inc.; Azmacort, active and placebo – Rhone-Poulenc Rorer.

Equipment Support:

Computer monitor, central processing unit, keyboard – S&M Instrument Company; Stadiometers – Seritex, Inc.; Airwatch Devices – Enact Health Management Systems; OptiChamber spacers – HealthScan.

IMPACT: Improving Asthma Control Trial

Supported by: Grants U10 HL 51831, U10 HL 51834, U10 HL 51843, U10 HL 51810, U10 HL 51823, U10 HL 51845, and U10 HL 56443 from the National Heart, Lung, and Blood Institute.

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Pharmaceutical Suppliers:

Pulmicort, active and placebo – AstraZeneca

Equipment Support:

Computer monitor, central processing unit, keyboard – S&M Instrument Company; Stadiometers – Seritex, Inc.; eDEM monitors – Aardex Ltd.

PRICE: Predicting Responses for Inhaled Corticosteroid Efficacy

Supported by: Grants U10 HL 51831, U10 HL 51834, U10 HL 51843, U10 HL 51810, U10 HL 51823, U10 HL 51845, and U10 HL 56443 from the National Heart, Lung, and Blood Institute.

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Pharmaceutical Suppliers:

QVAR, active and placebo – IVAX Inc.

Equipment Support:

Computer monitor, central processing unit, keyboard – S&M Instrument Company; Stadiometers – Seritex, Inc.;

SOCS; SLIC: Salmeterol Off Corticosteroids; Salmeterol ± Inhaled Corticosteroids

Supported by: Grants U10 HL 51831, U10 HL 51834, U10 HL 51843, U10 HL 51810, U10 HL 51823, U10 HL 51845, and U10 HL 56443 from the National Heart, Lung, and Blood Institute.

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Protocol Review Committee: Gary W. Hunninghake, MD (Chair), Iowa City, IA; Robert O. Crapo, MD, Salt Lake City, UT; Richard Nicklas, MD, Washington, DC; Robert C. Strunk, MD, St. Louis, MO; John E. Connett, PhD, Minneapolis, MI; William Kelly, Albuquerque, NM.

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Pharmaceutical Suppliers:

Ventolin, active and placebo – Glaxo Wellcome Inc.; Salmeterol, active and placebo – Glaxo Wellcome Inc.; Azmacort, active and placebo – Rhone-Puolenc Rorer; Allegra – Hoechst Marion Roussel.

Equipment Support:

Computer monitor, central processing unit, keyboard – S&M Instrument Company; Stadiometers – Seritex, Inc.; Airwatch Devices – Enact Health Management Systems.

CAMP Roster

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