ABSTRACT

Asthma is a common complex disease of the airways. Genome-wide association studies (GWAS) of asthma have identified many risk alleles and loci that have been replicated in worldwide populations. Although the risk alleles identified by GWAS have small effects and explain only a small portion of prevalence, the discovery of asthma loci can provide an understanding of its genetic architecture and the molecular pathways involved in disease pathogenesis. These discoveries can translate into advances in clinical care by identifying therapeutic targets, preventive strategies and ultimately approaches for personalized medicine. In this review, we summarize results from GWAS of asthma from the past 10 years and the insights gleaned from these discoveries.

Keywords: Asthma; genome-wide association study

INTRODUCTION

Asthma is a heterogeneous and genetically complex respiratory disease. Approaches for gene discovery in asthma were initially candidate gene association studies, followed by family-based genome-wide linkage analyses and, most recently, genome-wide association studies (GWAS). For the last decade, GWASs of asthma have dominated, providing bias-free discovery of novel risk loci.

The first GWAS of asthma was reported in 2007. As of July 10, 2018 there were 72 papers written in English on asthma or asthma-related traits reported in the GWAS catalog (https://www.ebi.ac.uk/gwas/). Among these 72 papers, 24 are GWASs of asthmatic subjects and controls, including 7 meta-analyses of asthma GWASs (Table 1); 5 are GWASs of asthma sub-phenotypes such as severe asthma or asthma exacerbations; 13 are GWASs of asthma-related traits such as bronchodilator response (BDR), airway hyperresponsiveness (AHR) and total serum immunoglobulin E (IgE) levels; 15 are GWASs of asthma combined with other diseases, such as allergic rhinitis, or factors such as smoking interaction or age of onset; 2 are GWASs of occupational asthma; 2 are GWASs of aspirin-exacerbated respiratory disease (AERD); and 11 are GWASs of asthma pharmacologic responses.
Table 1: Characteristics of GWASs of asthma

| Year | Author | Ethnicity | Sample size | No. genome-wide significant loci | Combined analysis | Reference |
|------|--------|-----------|-------------|---------------------------------|-------------------|-----------|
| 2007 | Moffatt MF | European | 5,639 subjects | Yes | 1 | NA |
| 2009 | Hancock RE | European | 295 subjects | Yes | 0 | NA |
| 2009 | Moffatt MF | European | 2,945 subjects | Yes | 2 | NA |
| 2010 | Bernstein FM | European | 6,037 subjects | Yes | 1 | 2 |
| 2010 | Truan BE | European | 1,776 subjects | Yes | 0 | NA |
| 2010 | Mathias RA | European | 8,550 subjects | Yes | 0 | NA |
| 2010 | Devalia AM | European | 3,106 subjects | Yes | 1 | NA |
| 2010 | McGee E | European | 41,400 subjects | Yes | 0 | NA |
| 2010 | Lasky-Su J | European | 2,352 subjects | Yes | 1 | NA |
| 2010 | Ferreira MA | European | 30,247 subjects | Yes | 2 | NA |
| 2010 | Galanter JM | European | 34,155 subjects | Yes | 1 | NA |
| 2010 | Nieuwenhuis MA | European | 986 cases and 1,846 controls | Yes | 0 | NA |
| 2010 | Hirota T | European | 1,532 cases and 3,304 controls | Yes | 0 | NA |
| 2011 | Moffatt MF | European | 75,842 subjects | Yes | 0 | NA |
| 2011 | Devalia AM | European | 2,538 subjects | Yes | 1 | NA |
| 2011 | McGee E | European | 25,358 subjects | Yes | 1 | NA |
| 2011 | Lasky-Su J | European | 30,395 subjects | Yes | 1 | NA |
| 2011 | Ferreira MA | European | 2,144 cases and 2,893 controls | Yes | 0 | NA |
| 2011 | Galanter JM | European | 7,977,792 controls | Yes | 0 | NA |
| 2011 | Nieuwenhuis MA | European | 803 cases and 1,564 controls | Yes | 1 | NA |
| 2011 | Hirota T | European | 2,352 cases and 4,031 controls | Yes | 0 | NA |
| 2012 | Devalia AM | European | 9,070 subjects | Yes | 0 | NA |
| 2012 | McGee E | European | 11,199 subjects | Yes | 0 | NA |
| 2012 | Lasky-Su J | European | 17,792 subjects | Yes | 0 | NA |
| 2012 | Ferreira MA | European | 1,716 cases and 16,888 controls | Yes | 0 | NA |
| 2012 | Galanter JM | European | 2,896 cases and 5,530 controls | Yes | 0 | NA |
| 2012 | Nieuwenhuis MA | European | 3,490 cases and 6,533 controls | Yes | 0 | NA |
| 2013 | Moffatt MF | European | 5,309 cases and 16,335 controls | Yes | 0 | NA |
| 2013 | Devalia AM | European | 1,574 cases and 3,145 controls | Yes | 0 | NA |
| 2013 | McGee E | European | 11,656 subjects | Yes | 0 | NA |
| 2013 | Lasky-Su J | European | 1,893 cases and 3,817 controls | Yes | 0 | NA |
| 2013 | Ferreira MA | European | 21,948 cases and 41,335 controls | Yes | 0 | NA |
| 2013 | Galanter JM | European | 8,193 cases and 1,564 controls | Yes | 0 | NA |
| 2013 | Nieuwenhuis MA | European | 27,030 subjects | Yes | 0 | NA |
| 2014 | Devalia AM | European | 1,893 cases and 3,817 controls | Yes | 0 | NA |
| 2014 | McGee E | European | 15,286 subjects | Yes | 0 | NA |
| 2014 | Lasky-Su J | European | 25,358 subjects | Yes | 1 | NA |
| 2014 | Ferreira MA | European | 2,144 cases and 2,893 controls | Yes | 0 | NA |
| 2014 | Galanter JM | European | 793 cases and 1,541 controls | Yes | 0 | NA |
| 2014 | Nieuwenhuis MA | European | 920 cases and 1,846 controls | Yes | 0 | NA |
| 2015 | Devalia AM | European | 920 cases and 1,846 controls | Yes | 0 | NA |
| 2015 | McGee E | European | 2,006 subjects | Yes | 0 | NA |
| 2015 | Lasky-Su J | European | 23,948 cases and 118,538 controls | Yes | 0 | NA |
| 2015 | Ferreira MA | European | 9,070 subjects | Yes | 0 | NA |
| 2015 | Galanter JM | European | 707 cases and 1,893 controls | Yes | 0 | NA |
| 2015 | Nieuwenhuis MA | European | 986 cases and 1,846 controls | Yes | 0 | NA |
| 2016 | Galanter JM | European | 28,399 cases and 128,843 controls | Yes | 0 | NA |
| 2016 | Devalia AM | European | 28,399 cases and 128,843 controls | Yes | 0 | NA |
| 2016 | McGee E | European | 25,358 subjects | Yes | 0 | NA |
| 2016 | Lasky-Su J | European | 25,358 subjects | Yes | 1 | NA |
| 2016 | Ferreira MA | European | 2,144 cases and 2,893 controls | Yes | 0 | NA |
| 2016 | Galanter JM | European | 793 cases and 1,541 controls | Yes | 0 | NA |
| 2016 | Nieuwenhuis MA | European | 920 cases and 1,846 controls | Yes | 0 | NA |
| 2017 | Devalia AM | European | 28,399 cases and 128,843 controls | Yes | 0 | NA |
| 2017 | McGee E | European | 25,358 subjects | Yes | 0 | NA |
| 2017 | Lasky-Su J | European | 25,358 subjects | Yes | 1 | NA |
| 2017 | Ferreira MA | European | 2,144 cases and 2,893 controls | Yes | 0 | NA |
| 2017 | Galanter JM | European | 793 cases and 1,541 controls | Yes | 0 | NA |
| 2017 | Nieuwenhuis MA | European | 920 cases and 1,846 controls | Yes | 0 | NA |
| 2018 | Devalia AM | European | 28,399 cases and 128,843 controls | Yes | 0 | NA |
| 2018 | McGee E | European | 25,358 subjects | Yes | 0 | NA |
| 2018 | Lasky-Su J | European | 25,358 subjects | Yes | 1 | NA |
| 2018 | Ferreira MA | European | 2,144 cases and 2,893 controls | Yes | 0 | NA |
| 2018 | Galanter JM | European | 793 cases and 1,541 controls | Yes | 0 | NA |
| 2018 | Nieuwenhuis MA | European | 920 cases and 1,846 controls | Yes | 0 | NA |

References are sorted by year. "Mixed" in childhood onset asthma denotes the unknown proportion of childhood onset asthma.

Specifications of the discovery stage genome-wide significant SNPs are in Supplementary Table S1. The replication data were shown in only the non-17q12-21 region. Bold loci are also genome-wide significant in the discovery GWAS; one locus from the results of the Australian GWAS only and seven loci from the results of the Australian GWAS and GABRIEL; both loci are also genome-wide significant in the discovery GWAS.

Loci including SNPs showing genome-wide significant association with asthma in at least one ethnic group; Meta-Analysis includes GWAS from references 5, 82, 84.

Loci including GWAS from references 5, 19, 88. 85, 90. Meta-Analysis includes GWAS from references 5, 19, 88, 85, 90.
GWAS of Asthma

In this review, we summarize the results of the 42 GWASs of asthma, asthma sub-phenotypes (e.g., severe asthma, asthma exacerbation) and asthma-related traits (e.g., BDR, AHR, total serum IgE) that are registered in the GWAS catalog. We discuss the challenges posed by GWASs of complex diseases and strategies to overcome these challenges. Other aspects of asthma genetics, such as gene-environment interactions,6–8 occupational asthma,9 AERD10,11 or pharmacogenetics12,13 are reviewed elsewhere.

GWAS of Asthma

Table 1 summarizes the study populations, sample sizes, and results of the 17 GWASs and 7 meta-analyses of asthma. Additional information on characteristics of the study populations is included in Supplementary Table S1.

Eight GWASs and 6 meta-analyses reported one or more association with genome-wide significance in the discovery population. Two additional GWASs reported genome-wide significant associations in a combined — discovery and replication — sample. These 16 studies together described 35 loci that were significant in at least 1 study (Tables 2 and 3, Supplementary Tables S2 and S3). Sixteen of the 35 loci showed nominal significance when replicated in other GWASs, and 14 of those 16 loci showed genome-wide significant associations in at least 2 papers. Taken together, 5 GWASs and 5 meta-analyses of asthma identified genome-wide significant single nucleotide polymorphisms (SNPs) (P < 5 × 10−8) at the 17q12-21 (ORMDL3, GSDMB), making this the most widely replicated asthma locus. The 6p21 (HLA region), 2q12

Table 2. Asthma susceptibility loci meeting criteria for genome-wide significance in either discovery or combined stage in each GWAS

| Year | Author | Region | Reported genes | Lead SNP | Location (Bp) | RAF in controls | P value OR | 95% CI | Stage | Replication | Reference |
|------|--------|--------|----------------|----------|---------------|----------------|----------|--------|-------|-------------|-----------|
| 2007 | Moffatt MF | 17q21 | ORMDL3 | rs726389 | 39913696 | NA | 1.00E-10 | NA | NA | Discovery | 7.94E-04 | 5 |
| 2010 | Sleiman PM | 1q31 | DENND1B | rs2796098 | 197356778 | 0.78 | 8.55E-09 | 1.59 | 1.28−1.81 | Discovery | 6.47E-04 | 77 |
| 2011 | Ferreira MA | 17q22 | ORMDL3 | rs4795400 | 39910767 | NA | 2.08E-08 | 1.28 | NA | Discovery | NA |
| 2011 | Noguchi E | 6p21 | HLA-DPB1 | rs987870 | 33075103 | 0.14 | 7.50E-09 | 1.51 | 1.31−1.74 | Discovery | 1.20E-02 | 83 |
| 2011 | Hirota T | 4q31 | USP38 | rs7686660 | 143082006 | 0.27 | 1.87E-12 | 1.16 | 1.11−1.21 | Combined | 3.33E-09 | 84 |
| 2011 | NJ0 | 1q43 | CDK2/KCIF4 | rs10508372 | 8930055 | 0.43 | 1.79E-15 | 1.16 | 1.12−1.21 | Combined | 1.31E-11 |
| 2012 | Lasky-Su J | 5p15 | FLJ25076 | rs270474 | 6482225 | NA | 3.78E-08 | NA | NA | Discovery | NA |
| 2012 | Galanter JM | 17q12 | IKZF3 | rs972346 | 32636595 | NA | 2.20E-08 | NA | NA | Discovery | 6.70E-03 |
| 2016 | White MJ | 10p12 | PTCHD3 | rs660498 | 274502030 | 0.46 | 2.20E-07 | 1.62 | 1.35−1.95 | Discovery | NA |

(continued to the next page)
| Year | Author(s) | Region | Reported genes | Lead SNP | Location (bp) | RAF in controls | P value | Stage | OR | 95% CI | Replication | P value | Reference |
|------|-----------|--------|----------------|----------|---------------|-----------------|--------|-------|----|--------|-------------|--------|-----------|
| 2016 | Nieuwenhuis MA | 17q21 | IZKF3/ILPBP2/GSDMB/ORMDL3 | rs2290400 | 39909987 | NA | 2.54–E-20 | 1.11–2.30 | NA | Combined | 6.78–E-17 | 89 |

**Meta-analysis**

| Year | Author(s) | Region | Reported genes | Lead SNP | Location (bp) | RAF in controls | P value | Stage | OR | 95% CI | Replication | P value | Reference |
|------|-----------|--------|----------------|----------|---------------|-----------------|--------|-------|----|--------|-------------|--------|-----------|
| 2010 | Moffatt MF | 2q12 | IL1RL1/IL1RL1/IL18R1/IL18RAP | rs7377166 | 102369762 | 0.62 | 3.40–E-09 | 1.15 | 1.10–2.30 | Discovery | NA | 19 |
| 2011 | Torgerson DG | 2q12 | IL1RL1 | rs7377180 | 102371575 | 0.86 | 1.50–E-15 | 1.20 | 1.11–2.20 | Combined | 5.30–E-07 | 19 |
| 2012 | Ramasamy A | 2q12 | IL1RL1/IL18R1 | rs13408661 | 102338629 | 0.84 | 1.00–E-09 | 1.23 | 1.11–2.30 | Combined | 3.20–E-05 | 91 |
| 2016 | Pickrell JK | 1q23 | ADAMTS4 | rs4233366 | 161183357 | NA | 4.80–E-15 | 1.09 | 1.07–1.11 | Discovery | NA | 21 |
| 2017 | Yan Q | 17q12 | IZKF3 | rs907092 | 39766006 | 0.68 | 1.16–E-12 | 1.41 | NA | Discovery | NA | 92 |
| 2017 | Almoguera B | 6p21 | GMR4 | rs7776893 | 34189667 | 0.47 | 5.29–E-09 | 1.25 | 1.19–1.31 | Discovery | NA | 34 |
| 2018 | Demenais F | 2q12 | IL1RL1 | rs4210101 | 102341256 | 0.27 | 3.9–E-01 | 1.12 | 1.09–1.15 | Discovery | NA | 14 |
| 6p21 | SLCS25A6 | rs3045502 | 110169301 | 0.34 | 9.4–E-26 | 1.15 | 1.12–1.30 | Discovery | NA | 18 |
| 6p21 | HLA-DRB1 | rs9272146 | 32636595 | 0.56 | 5.7–E-04 | 1.16 | 1.12–1.20 | Discovery | NA | 39 |

(continued to the next page)
GWAS of Asthma

Table 2. (Continued) Asthma susceptibility loci meeting criteria for genome-wide significance in either discovery or combined stage in each GWAS

| Year | Author | Region | Reported genes | Lead SNP | Location (bp) | RAF in controls | P value | OR | 95% CI | Stage | Replication | Reference |
|------|--------|--------|----------------|----------|---------------|-----------------|---------|----|--------|-------|-------------|-----------|
| 8q21 |        |        |                | rs2034381 | 80366650      | 0.66            | 1.1E-10 | 0.92 | 0.90–0.95 | Discovery | NA          |           |
| 9p24 |        |        |                | rs292969   | 6209697       | 0.75            | 7.2E-20 | 0.86 | 0.83–0.88 | Discovery | NA          |           |
| 10p14|        |        |                | rs2589561  | 9004682       | 0.82            | 3.5E-9  | 0.91 | 0.88–0.94 | Discovery | NA          |           |
| 11q3 |        |        |                | rs7927894  | 76592072      | 0.37            | 2.2E-14 | 1.1  | 1.08–1.13 | Discovery | NA          |           |
| 12q2 |        |        |                | rs167769   | 57109992      | 0.4             | 3.9E-9  | 1.08 | 1.05–1.11 | Discovery | NA          |           |
| 15q22|        |        |                | rs1071558  | 60777222      | 0.14            | 1.3E-9  | 0.89 | 0.86–0.92 | Discovery | NA          |           |
| 15q22|        |        |                | rs2033784  | 67157322      | 0.3             | 7.4E-15 | 1.1  | 1.08–1.13 | Discovery | NA          |           |
| 16p13|        |        |                | rs77806299 | 11106123      | 0.2             | 2.7E-10 | 0.91 | 0.88–0.94 | Discovery | NA          |           |
| 17q2 |        |        |                | rs2952156  | 397920582     | 0.7             | 2.2E-30 | 0.87 | 0.84–0.89 | Discovery | NA          |           |
| 17q21|        |        |                | rs1763472  | 49384071      | 0.39            | 6.6E-6  | 1.08 | 1.05–1.11 | Discovery | NA          |           |

The most significant SNPs at each locus are shown and ordered by genomic location in each reference. Base pair positions (bp) correspond to GRCh38/hg38 genome assembly.

SNP, single nucleotide polymorphism; RAF, risk allele frequency; OR, odds ratio; CI, confidence interval; FDR, false discovery rate; GWAS, genome-wide association study; GABRIEL, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community.

*With the exception of the 17q12-21 locus, none of the markers below 5% FDR, after controlling for stratification, were within 1 Mb of each other; †Discovery GWAS was the meta-analysis of results from the Australian GWAS and GABRIEL; ‡RAF was from the Australian GWAS only; §Discovery GWAS only; ¶P value from the Latino GWAS only; ‡‡Lead SNP.

A recent meta-analysis of 23,948 asthma cases and 118,538 controls from the Trans-National Asthma Genetic Consortium (TAGC) revealed 18 loci that met the criteria of genome-wide significance,14 including nine previously known asthma loci, 2 loci previously reported for asthma plus hay fever, 2 previously associated with asthma in ancestry-specific populations and 5 new asthma susceptible loci. The latter included loci at 5q31.3, 6p22.1, 6q15, 12q13.3 and 17q21.33. Nearly all of the lead SNPs at the new loci were located in noncoding regions, and some were expression quantitative trait loci (eQTL) for genes such as NDFIP1 (chromosome 5q31.3), ZSCAN12 and ZSCAN31 (6p22.1), BACH2 (6q15), STAT6 (12q13.3) and GNGT2 (17q21.33). An enrichment in enhancer marks, especially in immune cells, was found at the associated loci, suggesting that the associated SNPs, or SNPs in linkage disequilibrium (LD) with the associated SNPs, play a role in the regulation of the immune processes.

Since the first GWAS of asthma that identified variants at the 17q21 locus and the correlation of those variants with expression of ORMDL3,5 this region has been the most frequently studied and replicated locus. This region harbors a dense haploblock of SNPs that overlap at least 4 genes: IKZF3, ZPBP2, GSDMB and ORMDL3. The locus has since been extended to include regions flanking this core region, implicating PGAP3 and ERBB2 at the proximal end and GSDMA at the distal end as potentially representing independent asthma loci.15 Nineteen asthma GWASs overall reported associations with SNPs at the extended 17q12-21 locus (Table 3). Moffatt et al.16 carried out a subgroup analysis of childhood-onset asthma and reported the association of this region specific to childhood-onset asthma, but had few later-onset asthma individuals to separately analyze that subgroup in their consortium-based meta-analysis of asthma GWASs. The TAGC meta-analysis of asthma GWAS also showed that the 17q12-21 locus centered on ORMDL3/GSDMB was specific to early-onset asthma, while that SNPs at the PGAP3/ERBB2 loci were not.14 They also suggested that the asthma-associated signals near the PGAP3/ERBB2 and ORMDL3/GSDMB blocks may affect asthma risk through the expression of different genes in different tissues.14,15 Of note, the effects of genotype at this locus on asthma risk and protection have been reported to be modified by early-life exposures including environmental tobacco smoking17 and rhinovirus (RV)-associated wheezing in the first 3 years of life.18 Despite its
strong and consistent association with asthma, there has been little evidence of association at this locus in African ancestry populations,\textsuperscript{14,19} possibly owing to the breakdown of LD on African-derived chromosome.\textsuperscript{15} Taken together, SNPs in this locus are robustly associated with childhood-onset asthma in European, Asian and Latino individuals. Stein et al.\textsuperscript{17} recently reviewed studies of the 17q12-21 locus that showed the asthma-associated 17q12-21 SNPs are eQTLs for the \textit{GSDMA}, \textit{ORMDL3}, \textit{GSDMB} and \textit{PGAP3} in immune cells and/or lung cells. However, the role of 17q12-21 genes in asthma pathogenesis is still unknown. An overview of functional studies of genes at the 17q12-21 locus was reviewed recently by Das et al.\textsuperscript{20}

Among the approximately half of the published GWAS of asthma that did not identify any genome-wide significant associations in their discovery stage, most had sample sizes < 2,000 subjects (Table 1) suggesting that larger sample sizes (≥10,000) are needed to identify asthma associated loci. For example, the TAGC meta-analysis showed that pooling data from ethnically diverse populations including 23,948 asthma cases and 118,538 controls,\textsuperscript{14} and a

### Table 1. Locus-level replications in subsequent GWAS

| Reported genes | Region | The strongest SNP | P value | Reference |
|---------------|--------|------------------|---------|-----------|
| STAR031/TCAP/AGAP3/ERBB3/KZ1F3/ZPBP2/GSDMB/ORMDL3/GSDMA/ZNF652/PSMD3/MED24 | 17q12-21 | rs7216389 | 1.00.E-10 | 5 |
| CCHCR1/PBX2/NOTCH4/C6orf40/BTNL2/GRM4/HLA region/MICB/MICA | 6p21 | rs9273349 | 7.00.E-14 | 16 |
| IL1RL2/IL1RL1/IL1BR/IL1BRAP | 2q12 | rs7771166 | 3.40.E-09 | 16 |
| TSLP/WDR28/SLC25A46 | 8p24 | rs1043828 | 1.10.E-08 | 82 |
| IL33/RANBP6 | 15q22 | rs744910 | 3.90.E-09 | 16 |
| SMAD3/RORA | 5q31 | rs6871536 | 2.40.E-09 | 82 |
| RAD50/L13/NDFIP1 | 1q13 | rs7130588 | 1.80.E-08 | 82 |
| CTf1orf30/LRRC35/EMSY | 12q13 | rs701704 | 2.33.E-13 | 84 |
| IL2RB | 22q12 | rs2284033 | 1.20.E-08 | 16 |
| BACH2 | 8q15 | rs5852088 | 7.10.E-11 | 21 |
| TPD52 | 10p4 | rs12543811 | 1.10.E-10 | 21 |
| GATA3 | 16p13 | rs737806299 | 3.50.E-15 | 21 |
| CLEC7A | 1p32 | rs6620664 | 3.90.E-08 | 21 |
| DENND1B | 1q31 | rs7576094 | 8.55.E-09 | 77 |
| SLC30A4 | 8q24 | rs3019885 | 5.00.E-13 | 83 |
| PEX4 | 19q13 | rs6683383 | 1.10.E-08 | 21 |
| IL6R | 2p25 | rs3412757 | 1.30.E-08 | 21 |
| ADAM15 | 2q37 | rs34290285 | 1.80.E-15 | 21 |
| CD247 | 3q27 | rs2079098 | 4.42.E-09 | 19 |
| TNFSF4 | 3q28 | rs73196739 | 6.50.E-09 | 21 |
| ADORA1 | 4p14 | rs5743618 | 3.90.E-11 | 21 |
| - | 4q31 | rs7686660 | 1.87.E-12 | 84 |
| USP9B | 5p15 | rs729474 | 3.78.E-08 | 85 |
| FLJ25076 | 6p22 | rs1233578 | 5.90.E-07 | 14 |
| GPK5 | 7q22 | rs6953584 | 2.00.E-08 | 21 |
| CDHR3 | 9p21 | rs72721168 | 7.02.E-10 | 34 |
| EQTN | 10p12 | rs660498 | 2.20.E-07 | 88 |
| PTCHD3 | 14q13 | rs17441370 | 1.37.E-11 | 85 |
| AKAP9 | 14q24 | rs7264099 | 1.60.E-08 | 21 |
| RAD51B | 15q22 | rs6620664 | 3.90.E-08 | 21 |

The table is sorted by the most number of repeatedly replicated loci. There were no replication data of previously reported GWAS in references 5, 76, 79, 80.

Nominal replication signifies the SNPs at each locus with replication P value less than 0.05 when there were replication data of previously reported GWAS.

GWAS, genome-wide association study; SNP, single nucleotide polymorphism.
23andMe GWAS in 28,399 European ancestry cases and 128,843 controls each detected new asthma loci. Although very large studies increase clinical heterogeneity, many true asthma loci can be detected in very large samples.

GWAS OF ASTHMA SUB-PHENOTYPES AND INTERACTIONS

GWASs of asthma sub-phenotypes reduce heterogeneity and can lead to the identification of new asthma risk loci, even in smaller samples, due to increased power in studies of extreme or more homogeneous phenotypes. These studies may unveil genetic factors that are ‘masked’ in very large GWAS of more heterogeneous cases. For example, this is best illustrated by a GWAS of early childhood asthma with acute exacerbations leading to hospitalization and emergency department visit by Bønnelykke et al.\textsuperscript{22} The \textit{CDHR3} at 7q22.3 was identified in this study as a new susceptibility gene; this locus was later shown to be genome-wide significant in the 23andMe GWAS in European ancestry individuals,\textsuperscript{21} but not in the TAGC meta-analysis of ethnically diverse individuals.\textsuperscript{14} Importantly though, subsequent studies showed that \textit{CDHR3} functions as a receptor for Rhinovirus C (RV-C),\textsuperscript{23} and that the \textit{CDHR3} asthma risk allele was associated specifically with RV-C-related respiratory illnesses in the first 3 years of life.\textsuperscript{24} This “exacerbation GWAS” also confirmed previously reported asthma loci at genome-wide significance — \textit{GSDMB} at 17q21, \textit{IL33} at 9p24, \textit{RAD50} at 5q31 and \textit{IL1RL1} at 2q12 loci, but with larger effect sizes despite the smaller sample size (Table 2), demonstrating that careful phenotyping and reduced clinical heterogeneity can reveal both novel asthma loci and larger effects of associated loci in smaller sample sizes than typically required for GWAS.

Another GWAS of exacerbations in 2 pediatric cohorts reported a novel asthma locus at the 10q21.3 (\textit{CTNN4A}) that was genome-wide significant.\textsuperscript{25} A meta-analysis of GWASs that included both physician-diagnosed asthma and hay fever compared to controls with neither
asthma nor hay fever revealed 2 novel susceptible loci: ZBTB10 at 8q21.13 and CLEC16A at 16p13.13. A GWAS of asthma with reduced exposure to tobacco smoke identified a locus that included the gene, HAS2 at 8q24.13, as a susceptibility locus, and another GWAS of active adult-onset nonallergic asthma added novel loci to asthma susceptible genes, CD200 at 3q13.2 and GRIK2 at 6q16.3, compared to inactive and mild nonallergic asthma. A GWAS that investigated the age of onset of childhood asthma, revealed loci on 3p26 and 11q24 that were associated with early-onset asthma and potentially to more severe disease. These GWASs of asthma defined by the presence or absence of other conditions identify novel loci, but most still require replication and functional characterizations.

Another approach to disentangle the complexity of asthma phenotypes and account for potential heterogeneity of risk factors have been genome-wide interaction studies (GWISs). A GWIS of genotype-by-sex interactions revealed a male-specific asthma risk locus, which includes IRF1 at 5q31.1, in European ancestry individuals, and a female-specific asthma risk locus, which included RAP1GAP1 at 1p36.12, in Latino individuals. The SNPs at these 2 loci showed only nominally significant associations with asthma in an independent GWAS, but emerged as sex-specific asthma risk loci when the effects of both genotype and sex as an interaction were taken into account. Another GWIS of farm-related exposures on asthma and atopy risk did not show any significant associations with either novel or previously reported asthma loci, likely due to low statistical power. Although this is a promising approach to identify loci that may confer risk only in the presence of specific exposures (i.e., gene-environment interactions), it is challenging to conduct these studies in the very large samples because exposures histories are rarely available in those samples.

Finally, gene discovery in smaller samples may be possible using validated phenotyping algorithms that mine electronic medical records (EMRs). This approach has recently been developed as a tool for genomic research by the Electronic Medical Records and Genomics (eMERGE) network. A GWAS of asthma in 5,309 cases and 16,335 controls recruited from eMERGE network identified novel loci of 6p21.31 (GRM4) and 9p21.2 (EQTN), although these associations need further replication and functional characterization. Within EMRs, longitudinal phenotype data and immense amounts of secondary phenotype data, such as laboratory findings and drug responses, can be collected. These data can be analyzed along with genetic data to determine whether loci are specific to asthma or shared with other allergic phenotypes, or how these relationships change over time. Rapid adoption of EMRs and EMR data standardization across hospitals will make available extensive phenotype data on many diseases and, combined with patient genotyping, expedite the identification of shared and unique genetic signatures for asthma endotypes as well as all common diseases.

GWAS OF ASTHMA-RELATED TRAITS

GWASs have been reported for asthma-related traits such as BDR, AHR, blood eosinophils, total serum IgE levels and allergic sensitization. The general assumptions of these studies are that it may be easier to find genes influencing components of asthma because they are less heterogeneous than asthma per se, and those same genes may also contribute to asthma risk and potentially provide more direct pharmacologic targets.

A GWAS of BDR — defined as the percentage change in FEV1 after administration of a short-acting β2-adrenergic receptor agonist — identified rare variants (frequency, <5%)
near the solute carrier (SLC) genes with genome-wide significance in 1,782 Latino asthmatic children. Another GWAS of BDR revealed genome-wide significant variants near the ASB3 gene at 2p16 in a combined analysis of 1,164 multi-ethnic individuals with asthma. A GWAS of AHR severity — defined as the natural log of the dosage of methacholine causing a 20% drop in FEV1 — in 994 non-Hispanic white asthmatic subjects did not identify any genome-wide significant genes, while another GWAS of AHR severity in 650 European adult asthmatics revealed SNPs at the PDE4D gene at 5q11 at genome-wide significance, which is a previously reported asthma gene. Overall however, the BDR and AHR genes identified in GWAS with relatively small sample sizes lack replication. In contrast, a large GWAS of blood eosinophils, pleotropic multifunctional leukocytes that are involved in the pathogenesis of inflammatory diseases including asthma, in 21,510 European subjects (comprised of a discovery, n = 9,392, and replication, n = 12,118, sample) reported SNPs near the IL1RL1 at 2q12, IKZF2 at 2q34, GATA2 at 3q21.3, IL5 at 5q31.1 and SH2B3 at 12q24.12 genes with genome-wide significance. Among them, a variant at IL1RL1 was also associated with asthma in 10 different populations included in this study. IL1RL1 has been reported as an asthma gene through multiple GWAS of asthma (Tables 2 and 3). This finding requires further functional characterization if its relationship to eosinophils, asthma, and especially eosinophilic asthma, and its potential as a therapeutic target.

The first GWAS of total serum IgE levels, which is a strongly heritable trait, did not show any genome-wide significant associations in the discovery population of 1,530 individuals of European ancestry. However, by combining the GWAS results with 4 independent replication cohorts, the investigators showed that functional variants near the gene encoding FCERIA at 1q23.2 and at the RAD50-IL13 locus at 5q31 were associated with total serum IgE levels at genome-wide significant thresholds in a combined analysis in of 11,299 individuals of European ancestry. The Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) consortium identified SNPs near HLA-DRB1 at 6p21 as an IgE-associated locus that was independent of associations of this locus with asthma, and confirmed the previously reported associations between total serum IgE levels and SNPs near the FCERIA, RAD50-IL13 and STAT6 loci, at genome-wide significant level. Three more GWAS of total serum IgE levels revealed loci near the HLA region reaching genome-wide significance; the EVE consortium confirmed that these associations were shared among diverse ethnic groups. A GWAS of total serum IgE levels in 3,334 Latinos and a following admixture mapping in 454 Latinos, 1,564 European Americans and 3,187 African Americans revealed a locus near the ZNF365 gene at 10q21, but this finding still lacks replication. Furthermore, a meta-analysis of GWASs of allergic sensitization in 15,845 individuals of European ancestry and replication in 16,034 individuals of European ancestry identified 10 genome-wide significant loci in or near TLR6 at 4p14, C1orf30 at 11q13, STAT6 at 12q13, SLC25A46 at 5q22, HLA-DQB1 at 6p21, IL1RL1 at 2q12, LPP at 3q28, MYC at 8q24, IL2 at 4q27 and HLA-B at 6p21. A recent GWAS of allergic disease in 360,838 individuals considered individuals with asthma, hay fever and/or eczema. They identified 136 genome-wide significant risk variants at 99 independent loci, most of which had similar effects on the individual diseases, reflecting etiologic pathways that are common to all 3 diseases. However, this did not explicitly test for independent effects of the associated loci among individuals with only one of the three diseases. The shared loci were predicted to influence the function of immune cells and their target genes suggested opportunities for genomics-guided drug repositioning.
FUNCTIONAL STUDIES OF ASSOCIATED SNPS FROM EXISTING GWAS

A limitation of GWAS is that it identifies SNPs but does not provide information on the genes that the associated SNPs influence or on the causal SNP(s) among all SNPs in strong LD. As a result, nearly all GWASs report the nearest gene(s) as potential asthma candidate genes. However, not all SNPs impact the function or expression of the nearest gene, even when the SNP is within the gene itself. For example, among disease-associated variants that are eQTLs, the target gene will differ from the nearest gene 34% of the time.\(^5\) On the other hand, SNPs that are eQTLs are more likely to be among significant GWAS SNPs compared to SNPs that are not eQTLs,\(^6\) and combining eQTL mapping with GWAS can link GWAS-associated variants with the gene(s) they regulate, particularly if studies are performed in disease-relevant tissues.\(^7\) For example, Li et al.\(^5\) performed \(cis\)-eQTL studies in human bronchial epithelial cells (BECs) and cells from bronchial alveolar lavage (BAL) using SNPs near 34 putative asthma genes at 23 loci from previous GWASs. SNPs at 9 of the 23 loci were associated with the expression of nine genes in either BEC or BAL: \(IL1RL1\) (but not \(IL18R1\)) at 2q12, \(TSLP\) (but not \(WDR36\)) at 5q22, \(HLA-DQB1\) at 6p21, \(CDHR3\) at 7q22, \(ZBTB10\) at 8q21, \(IL33\) at 9p24, \(C11orf30\) (but not \(LRRC32\)) at 11q13, \(DEXI\) (but not \(CLEC16A\)) at 16p13, and \(GSDMB\) (but not \(ORMDL3\)) at 17q21. There are likely to be additional \(cis\)-eQTLs at asthma-associated SNPs at some of these loci in other tissues or by considering more SNPs or genes at each locus.

Ferreira et al.\(^5\) used a gene-based association test that integrated published asthma GWAS and eQTL mapping studies to identify SNPs that are eQTLs and the genes they are associating with. They used 16 published eQTL studies in 12 cell types or tissues potentially relevant to asthma: whole blood, lymphoblastoid cell lines, peripheral blood mononuclear cells, monocytes, B cells, T cells, neutrophils, spleen, lung, small airways, fibroblasts, skin. They suggested that asthma risk was associated with the expression of genes related to nucleotide synthesis (\(B4GALT3\) at 1q23.3 and \(USMG5\) at 10q24.33) and nucleotide-dependent cell activation (\(P2RY13\) and \(P2RY14\) at 3q25.1), and referred to these genes as putative novel asthma risk genes. They applied this method to their recent large GWAS of allergic disease,\(^8\) and identified additional significant and reproducible gene-based associations with 19 genes at 11 loci that were missed by single-variant analyses reported in the previous GWASs.\(^4\) Among these were nine genes with known functions relevant to allergic disease: \(FOSL2\) at 2p23, \(VRBP\) at 3p21, \(IPCEF1\) at 6q25, \(PRRS1\) at 11p13, \(NCF4\) at 22q12, and \(APOBR, IL27, ATXN2L\) and \(LAT\) at 16p11. These putative novel associations still need further replication. Luo et al.\(^5\) combined asthma GWAS results and publicly available eQTL data from human epithelial cells from small and large airways. They demonstrated that asthma GWAS hits were enriched as airway epithelial eQTLs and genes regulated by asthma GWAS loci in epithelium were enriched in immune response pathways. Li et al.,\(^5\) Ferreira et al.,\(^5\) and Luo et al.\(^5\) linked asthma-associated SNPs to genes they regulate, potentially elucidating molecular mechanisms for their associations with asthma.\(^5\) A great boon to this type of approaches is the Genotype-Tissue Expression (GTEx) consortium, which has made available eQTL data for 44 human tissues that can be used to identify genes and pathways affected by human disease-associated variation.\(^5\)

GWAS OF ASTHMA OR ASTHMA-RELATED TRAITS IN THE KOREAN POPULATION

In 2008, the first GWAS of an asthma phenotype in 347 Korean subjects (84 cases and 263 controls) was published for toluene diisocyanate (TDI)-induced asthma, an occupation-
associated form of asthma. Since then, GWASs of asthma in Korea focused on 80, 100, 117 and 179 subjects with AERD, which is characterized by the development of bronchoconstriction in asthmatic patients after ingestion of non-steroidal anti-inflammatory drugs including aspirin. However, no genome-wide significant loci were reported in these GWASs, likely due to small sample sizes.

A GWAS of total serum IgE levels was reported in 877 Korean asthmatic patients without any genome-wide significant hits, but a GWAS of asthma in the Korean population has not yet been published. Performing GWASs of asthma in Korean children and adults is called for in the near future in order to identify the major genetic susceptibilities that maybe unique to this population.

**ISSUES AND CHALLENGES IN GWAS OF ASTHMA**

Despite their power for identifying asthma risk loci, there are many limitations of GWASs. In particular, GWASs identify mostly common variants which tend to have small effect sizes. As a result, GWAS-discovered variants are largely common (MAF > 10%) and account for a small proportion of both the population prevalence and the genetic component of asthma (i.e., the heritability). These results in limited predictive power of these variants. Although rare and low-frequency variants have potentially larger phenotypic effects, they have not explained a significant fraction of the ‘missingness’ of asthma heritability thus far. Recently, in a whole-genome sequencing study, Smith et al. found a rare loss of function mutation in IL33 that was associated with both lower blood eosinophils in 103,104 European subjects and reduced risk of asthma in 6,465 European asthmatic subjects and 302,977 controls. This study suggests that rare variants with large effect sizes are segregating in the population. While it is unlikely that such rare variants will account for significant proportions of the population risk for asthma, they can identify new pharmacologic targets and therefore serve a very important function.

Another limitation of GWAS is the statistical approach that tests for association with each of potentially tens of millions of SNPs. As a result, adjustments for multiple testing, typically using a Bonferroni corrected P value of $5 \times 10^{-8}$ to control the false positive rate, require very large sample sizes (potentially >100,000) to identify loci with modest effect sizes. This stringent significance threshold will miss many true associations, particularly with SNPs involved in gene-gene and gene-environment interactions or those that are associated with specific asthma endotypes or sub-phenotypes. These variants have been referred to as ‘mid-hanging fruit’ in GWAS, and differentiating true from false associations among variants with small P values (e.g., $<10^{-4}$) that do not meet genome-wide significance thresholds in GWASs remains a major challenge.

Another limitation has been that most GWAS and large meta-analyses of asthma and related traits are in subjects of European ancestry. Thus, most inferences about the genetic architecture of asthma is based on observations in this one continental population, whereas much less is known about Asian, African and admixed populations. Because populations vary with respect to allele frequencies, patterns of LD, and effect sizes of variants that underlie disease risk, inferences based on Europeans may have limited utility in other groups. For example, next-generation sequencing studies revealed differences in allele frequencies and haplotype structures at the 17q12-21 asthma-locus between Chinese and other ethnic groups. However, half of the 24 asthma GWAS are only in Europeans (Table 1), and those studies are in
general the largest GWAS to date. Moreover, until recently, commercial genotyping arrays were based on European allele frequencies and LD patterns. As a result, GWAS in non-European populations likely missed variants specific to those populations. This also impacts the selection of tag SNPs in replication studies in non-European populations. These issues have recently been addressed by the development of ethnic-specific and pan-ethnic genotyping arrays and publicly available genome sequences that allow for ethnic-specific imputation of genome-wide SNPs.\(^\text{74}\) For the first time, GWAS in Asian, Latino and African populations can be performed with excellent SNP coverage. It is crucial to study populations of diverse ethnic backgrounds for identifying shared and unique genetic predictors of asthma and for capturing more global patterns of genetic risk and gene-environment interaction effects on asthma risk.

## CONCLUSIONS

Asthma pathogenesis is complex, resulting from heterogeneous genetic and environmental factors that jointly give rise to extensive phenotypic heterogeneity among asthmatics. Age at time of exposure to environmental risk factors and the persistence of these exposures during the lifespan may be critical modifiers of genotype-specific risk. These considerations are rarely, if ever, accounted for in GWAS. Nonetheless, the identification of susceptibility variants has already provided mechanistic insights into asthma pathogenesis, suggesting that asthma risk variants play a role in the regulation of immune cell functions.\(^\text{14}\) GWAS findings, considered together with deep learning approaches that can incorporate longitudinal EMR data,\(^\text{75}\) have the potential to more fully elucidate the genetic architecture of asthma. Such insights can be translated into advances in clinical care through identifying therapeutic targets and preventive approaches and ultimately personalized medicine.\(^\text{67}\)

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## SUPPLEMENTARY MATERIALS

### Supplementary Table S1
Characteristics of the study populations of GWAS of asthma

[Click here to view](#)

### Supplementary Table S2
Asthma susceptibility SNPs that met criteria for genome-wide significance in either discovery or combined stage in each GWAS

[Click here to view](#)
Supplementary Table S3
Asthma susceptibility SNPs that met criteria for genome-wide significance in meta-analyses

Click here to view

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