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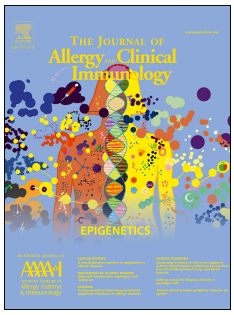

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Advances in Asthma and Allergic Disease Genetics – Is Bigger Always Better?

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Abbreviations

CanPAR, Canadian Peanut Allergy Registry

CAAPA, Consortium on Asthma among African Ancestry Populations

COPD, chronic obstructive pulmonary disease

EAGLE, Early Genetics and Lifecourse Epidemiology

eQTL, expression quantitative trait locus

GALA, Genes, Environments and Ancestry in Latino Americans

GERA, Genetic Epidemiology Research in Adult Health and Aging

GWAS, genome-wide association study

LD, linkage disequilibrium

SAGE, Study of African Americans, Genes and Environment

SAPPHIRE, Study of Asthma Phenotypes and Pharmacogenetic Interactions by Race-Ethnicity

TAGC, Trans-National Asthma Genetics Consortium

TOPMED, Trans-Omics for Precision MEDicine

Abstract:

This review focuses on genome-wide association studies (GWASs) of asthma and allergic diseases published between January 1, 2018 and June 30, 2019. During this time period there were 38 GWASs reported in 19 papers, including the largest performed to date for many of these conditions. Overall, we learned that childhood onset asthma is associated with the most independent loci compared to other defined groups of asthma and allergic disease cases; adult onset asthma and moderate-to-severe asthma are associated with fewer genes, which are largely a subset of those associated with childhood onset asthma. There is significant genetic overlap between asthma and allergic diseases, particularly with respect to childhood onset asthma, which harbors genes that reflect the importance of barrier function biology, and to HLA region genes, which are the most frequently associated genes overall in both groups of diseases. Although the largest GWASs in African American and Latino/Hispanic populations were reported during this period, they are still significantly underpowered compared to studies reported in European ancestry populations, highlighting the need for larger studies, particularly in childhood onset asthma and allergic diseases, in these important populations that carry the greatest burden of disease.

The past 18 months have witnessed tremendous strides in our understanding of the genetic architecture of asthma and allergic diseases. These advances are primarily the result of increasingly larger GWASs that have facilitated the discovery of more risk loci overall and, for the first time, the ability to perform large GWAS within both ethnically diverse populations and phenotypic subgroups of these conditions. The availability of publicly available sources of large data sets, such as the UK Biobank[1], and the many large-scale collaborations that combined smaller data sets for meta-analyses have resulted in significant gains of power to detect disease-associated loci and allowed us to begin to dissect the genetics of clinical heterogeneity and of racial disparities, two cardinal features of these diseases. This review highlights the GWASs published on asthma and allergic diseases –with focus on atopic dermatitis, allergic rhinitis and food allergy– between January 1, 2018 and June 30, 2019, drawing from them the novel insights and discoveries made during this time period.

Overview of Lessons Learned: Bigger is Not Always Better

The common dogma about sample sizes for genetic studies that "bigger is better" is based on the realization early on that genetic variants contributing to risk for asthma and allergic diseases have small effects and, therefore, will be detected only in very large samples. Moreover, because of the substantial multiple testing burden in genome-wide studies, large samples sizes are needed to obtain p-values that meet criteria for genome-significance (typically at $P < 5x10^{-8}$). While it is generally true that bigger is better, the quest for larger and larger samples is a double-edged sword, with trade-offs between gain of power due to larger samples and loss of power due to increased clinical, environmental, and genetic heterogeneity among cases, an inherent feature of

very large samples. These trade-offs are well illustrated by the GWASs of asthma and allergic diseases published over the period covered in this review.

The relationship between sample size and number of loci discovered by GWAS or genome-wide admixture mapping for asthma and allergic diseases, or their sub-phenotypes, performed over the last 18 months provide general insights that can inform the design of future studies. First, GWASs in samples with fewer than 5,000 cases (indicated by a dashed horizontal line in **Figure 1**) are unlikely to yield more than one or two genome-wide significant loci, at best, indicating that sample sizes in this range lack power to detect most disease-associated variants. Second, studies in admixed or multi-ancestry populations[2, 3] reveal fewer genome-wide significant loci than those in similarly sized samples comprised solely of European ancestry populations, likely reflecting increased genetic and environmental heterogeneity in these samples. Third, studies in well-defined subgroups of asthma, such as childhood onset[4, 5] or moderate-to-severe[6] asthma, yield more significant loci compared to GWAS of "asthma" with similar numbers of cases, presumably due to decreased clinical heterogeneity in those subgroups. Other considerations, such as the number of controls, the true contribution of genetics to phenotypic variation (i.e., heritability), and the precision of phenotyping, also contribute to the relative successes of GWASs. Lastly, variants in the HLA region are the most frequently associated with both asthma and allergic phenotypes (**Figure 2**), In fact this was the very first genetic locus linked to and associated with asthma and allergic disease[7-12]. These early studies demonstrated the specificity of those associations with individual allergens and between asthma and allergy, findings that are supported by the current studies discussed below.

In the following sections, we will overview the 38 GWASs published in 19 papers over the past 18 months, highlighting their unique contributions to our understanding of the genetic

basis for asthma and allergic disease. Summaries of the loci reported in these 38 GWAS are shown as a word cloud in **Figure 2** and the genes at those loci listed in **Table 1**.

GWASs of "Asthma" in Ethnically Diverse Populations

Four GWAS of asthma were published during the period covered by this review, and all included ethnically diverse subjects (**Figure 1**). The definition of asthma in these studies was based on a "doctor's diagnosis", either by physician or self-report [2, 3, 13] or by electronic medical record searches[14]. Three included children and adults[2, 3, 13], but with predominantly childhood onset asthma cases, and one included only adults (age ≥ 21 years) with unspecified ages of asthma onset[14]. Three performed meta-analyses both within and between ethnic/racial groups[2, 3, 13] and one performed GWASs separately within each sample[14]. Two included ethnically-matched replication samples[3, 14], and one performed genome-wide admixture mapping[3].

Demenais *et al*[13] published meta-analyses of GWASs in ethnically and racially diverse populations included in the Trans-National Asthma Genetic Consortium (TAGC). This represented the largest GWAS of asthma at the time of its publication, including 23,948 subjects with European, African, Japanese or Latino ancestry. Combining individual GWASs within and then across the four groups by meta-analysis enabled the discovery of 18 genome-wide significant loci in a multi-ethnic analysis, doubling the number of loci identified in previous large meta-analyses[13, 15] and including nearly all previously reported asthma loci. The five most significant loci in both the multi-ancestry and European ancestry meta-analyses were at well-replicated asthma loci on chromosomes 17q12-21 near *PGAP3* and *ERBB2*, 6p21.32 near *HLA-DRB1*/*-DQA1*, 5q22.1 near *TSLP*, 2q12 near *IL1RL1*/*IL18R*, and 9p24.1 near *IL33*. Sub-setting

on subjects with reported onset of asthma ≤18 years of age revealed the same five most significant loci, although the most significant variants at the 17q12-21 locus in the early onset cases were nearest to *GSDMB* and *ORMDL3*, consistent with earlier GWASs[15-17]. Thus, most of the loci identified in this study were robust to ethnicity and age of asthma onset. Among the 18 loci, five had not been reported in previous GWASs and were considered novel asthma-susceptibility loci whereas two were new loci for asthma at regions that were previously associated with asthma + hay fever[18, 19]. The latter reflects potential shared genetic risk between asthma and hay fever[20], which is discussed below in more detail[21, 22].

Several novel insights were made by the TAGC investigators. First, the majority of the associated variants, which were in non-coding regions of the genome (as in all GWASs of asthma and other complex phenotypes), were enriched in regions of the genome that are annotated as enhancers, particularly in lymphocytes and monocytes. This suggests that a substantial portion of the genetic risk for asthma is mediated by regulation of gene expression in immune cells. Second, there was significant overlap of the novel asthma loci with regions identified in GWASs of allergic, lung function, and other immune-related disease phenotypes, suggesting a shared genetic architecture among these conditions. Third, the investigators tested more broadly for evidence of pleiotropy between asthma and all diseases in the GWAS Catalogue[23]. After accounting for linkage disequilibrium (LD) between variants, they showed that asthma-associated variants overlapped with a wide range of diseases beyond those typically considered to be allergic or immune-mediated, including conditions as disparate as cardiovascular disease, neuropsychiatric disorders, and cancers, possibly reflecting the omnigenic nature of most common diseases[24]. Lastly, although the TAGC investigators studied diverse populations, there was not sufficient power to detect ancestry-specific associations.

Rather, all groups contributed to most of the GWAS signals, although with varying effect sizes between groups at some loci.

The Genetic Epidemiology Research in Adult Health and Aging (GERA) investigators conducted four separate GWAS in non-Hispanic white, African American, Hispanic, and Asian adults. In this study, Dahlin, Sordillo *et al*[14] used medical records from Kaiser Permanente Northern California health care system to classify individuals as asthma cases or controls. The only GWAS that included more than 5,000 cases was that in the non-Hispanic white subjects (n=16,275 cases), which nonetheless revealed only two genome-wide significant loci, one at the *IL1RL1*/*IL18R* locus on chromosome 2q12.1 and one at the *HLA-DQA1/-DQB1* locus on chromosome 6p21.32, two well-known and highly replicated asthma loci. One other genome-wide significant locus at chromosome 2q32.2 near the *COL3A1* gene was reported in the African American GWAS (n=1,320), but this finding was not replicated in independent samples from the GABRIEL[17] and EVE[15] consortia, both component studies of the TAGC meta-analysis[13] discussed above. The paucity of significant findings, particularly in the non-Hispanic white GWAS, may be due to the clinical heterogeneity in this sample of adults, which used a broad case definition to include physician-diagnosed asthma, self-reported asthma, or report of an asthma exacerbation. This sample likely included cases with both childhood onset and adult onset asthma, although the lack of association at the 17q12-21 locus suggests that this sample was comprised mostly of adult onset asthma, which has a smaller genetic component and more shared genetic architecture with other co-morbidities than childhood onset asthma, as discussed below[4, 5].

Two meta-analyses of asthma GWASs were conducted in admixed populations that have been significantly underrepresented in large GWASs. Daya *et al*[2] published the largest GWAS to

date in African ancestry populations from the Consortium on Asthma among African Ancestry Populations (CAAPA) study. Variants in two regions, 17q12-21 and 8p23, were genome-wide significant in a meta-analysis of 7,009 cases and 7,645 controls. Thus, this study in admixed individuals replicated the childhood onset asthma locus at 17q12-21, as well as highlighted differences in the genetic architecture and LD patterns at this important locus in populations with varying amounts of African ancestry. In particular, they reported an inverse association between proportion of African ancestry and evidence for association at this locus among their samples, and therefore concluded that the association at 17q12-21 in their study was largely driven by the European ancestry present at this locus in their samples. The associated variants at a novel locus on 8p23 were within an intron of a long non-coding RNA gene but the association could not be replicated in an independent sample of African Americans. Whether lack of replication was due to insufficient power in the smaller sample used for replication or to type 1 error in the CAAPA meta-analysis remains to be determined.

Gignoux, Torgerson *et al*[3] used admixture mapping meta-analyses to identify asthma-associated variants in 3,902 Hispanic/Latino, African American, and African Caribbean individuals from the EVE consortium[15] in their primary analysis, and used 3,774 Latino subjects from the Genes, Environments and Ancestry in Latino Americans (GALA) II study as replication cohorts. A single locus at 18q21 was genome-wide significant in the primary analysis and replicated in the GALA II sample. Interestingly, this locus was associated with increased risk of asthma in Latinos with Native American ancestry, but with reduced risk of asthma in Latinos with European ancestry. Proportion of African ancestry *per se* was not associated with risk. This finding raises the possibility that the effects of variation at some loci can be ethnic-specific and potentially modified by genetic background, which itself differs between populations with

different ancestry. Fine mapping at the 18q21 region further suggested that variation near the *SMAD2* gene was underlying the risk observed in Mexicans, the group with the largest proportion of Native American ancestry. Although only one locus was significantly associated with asthma, this study highlights the importance of studies in non-European populations and of using admixture mapping as a complementary approach to GWAS. The ancestry-specific effects of alleles at this locus resulting in opposite effects on risk in different ancestral groups may be why this locus has not been identified in other GWASs and raises the possibility that other loci with ancestry-specific effects may be identified in future, larger studies of admixed populations.

Together, these four studies highlight the challenges of discovering asthma loci in admixed populations, which harbor a disproportionate burden of asthma and its complications[25-28]. Larger samples with more refined phenotyping, as well as creative approaches for utilizing the unique features of these populations, will be required to fully characterize the genetic architectures of asthma and related phenotypes in these groups.

GWASs of Asthma Age of Onset

Childhood onset asthma and adult onset asthma differ with regard to severity, remission, comorbidities and sex ratios[29, 30]. While the lead variants at the most highly replicated asthma locus at chromosome 17q12-21 have been robustly associated with early-life asthma[15-17], other loci with age of onset effects had not been described. Two recent studies used genotype and phenotype data from the UK Biobank to expand on these earlier observations and dissect genetic risk factors for asthma onset at various ages[4, 5]. The Pividori, Schoettler *et al* study[4] performed three GWASs: one for asthma onset before age 12 years (childhood onset, n=9,433), one for

asthma onset between ages 26 and 65 years (adult onset, n=21,564); and one in the cases only considering asthma age-of-onset as a quantitative trait (n=37,846). The 318,237 controls for the first two GWASs were adults without a diagnosis (ever) of asthma. Individuals with COPD, chronic bronchitis, or emphysema were excluded from both the adult onset asthma cases and the shared controls. The Ferreira *et al*[5] study included 13,962 subjects with asthma diagnosed before the age of 19 years in a childhood onset GWAS and 26,582 subjects between ages 20 and 60 years in an adult onset asthma GWAS, excluding individuals with diagnoses of COPD or other respiratory disease. They also used a shared set of 300,671 controls that included individuals without a diagnosis of any allergic disease (asthma, hay fever, eczema, or other allergies).

Overall, the Pividori, Schoettler *et al*[4] study revealed 61 independent asthma loci, 56 in the childhood onset GWAS, 19 in the adult onset GWAS, and 19 in the age-of-onset GWAS. The 19 age-of-onset loci were a subset of the childhood onset loci. Twenty-eight of the 61 loci had not been previously reported to be associated with asthma. Among the 61 loci, 23 were specific to childhood onset asthma, one was specific to adult onset asthma, and 37 were shared. The Ferreira *et al*[5] study reported 142 genome-wide significant loci overall, with 123 loci associated with childhood onset asthma and 56 associated with adult onset asthma. Of these, 132 replicated at a $P < 0.05$ with the same direction of effect in a previous large GWAS of asthma[31]; 28 of the 132 replicated variants loci were not reported as genome-wide significant in previous asthma GWASs. Using publicly available expression quantitative trait loci (eQTL) data[5] or a transcriptome-wide gene-based association test[4], both studies linked asthma-associated variants to the genes they potentially regulate, providing a rich catalog of asthma candidate genes, some specific to childhood onset or adult onset asthma, for future functional studies.

The greater number of loci reported for childhood onset asthma in Ferreira *et al* is likely due to using a broader definition of childhood onset asthma (up to age 18 vs. 12 years in Pividori, Schoettler *et al*) and the resulting larger sample size, and possibly increased power due to exclusion of subjects with allergic diseases from the controls. The differences between the two studies for variants at the 17q12-21 locus with respect to both the absolute *P*-values and the relative significance compared to other loci in the childhood onset GWAS likely resulted from the inclusion of older (post-puberty) children in the Ferreira *et al* study because this locus has been shown to be most relevant in very early life[16, 32, 33]. Moreover, the variant with the greatest effect size on childhood asthma in the Pividori, Schoettler *et al* study at the *FLG* (filaggrin) locus (odds ratio [OR] = 1.97, 95% CI 1.82, 2.13; $P = 1.88 \times 10^{-65}$) was not identified in the Ferreira *et al* study. Although the effect size of this association was reduced after excluding 3,205 childhood onset asthma cases and 5,785 controls with reported allergic rhinitis, atopic dermatitis, or food allergy, the effect size of the *FLG* locus remained the largest overall (OR = 1.61, 95% CI 1.49, 1.74; $P = 2.45 \times 10^{-19}$) in the Pividori, Schoettler *et al* study, suggesting that the inclusion of older ages of onset in the Ferreira *et al* study may have diluted the effects of this locus as well.

Pividori, Schoettler *et al* also tested for tissue-specific enrichment of genes that mapped to childhood onset loci, and separately, for adult onset loci. Genes at childhood onset loci were more highly expressed in skin, whole blood and small intestines compared with other tissues, and genes at adult onset loci were more highly expressed in lung, whole blood, small intestines and spleen. Therefore, while there was overlapping enrichment of highly expressed genes in whole blood and small intestines, genes at adult onset loci were more highly expressed in the lung and spleen, an immune organ rich in lymphocytes, suggesting that adult onset asthma is more lung-centered and immune-mediated disease. In contrast, tissue-specific enrichments for expression of

genes at childhood onset asthma point to the skin, an epithelial barrier, indicating that onset of asthma in childhood results from barrier function defects that alter innate immune responses.

Ferreira *et al* showed genetic correlations between childhood onset and adult onset asthma with many other traits with publicly available GWAS results, similar to the TAGC study[13] but here addressing differences with respect to age of onset. For example, similar negative genetic correlations were observed for lung function traits with both childhood onset and adult onset asthma, whereas a positive genetic correlation with eczema was present in childhood onset asthma only. In contrast, genetic correlations were significantly greater for six sets of traits with adult onset asthma compared to childhood onset asthma. Positive correlations were observed between adult onset asthma and obesity-related traits, smoking (ever), rheumatoid arthritis, insomnia, and depressive symptoms; a negative correlation was observed between adult onset asthma and age when first child was born. These results further suggest that adult onset asthma may be a more heterogeneous condition than childhood onset asthma, with the former sharing genetic risk with a number of different co-morbidities.

Despite some differences, both studies using the UK Biobank data showed that the overall contributions of genetic variation and the effect sizes at individual loci are larger for childhood onset asthma compared to adult onset asthma. This likely reflects a more important role for environmental factors, increased clinical heterogeneity, and more co-morbidities associated with asthma diagnosed at later ages. Importantly, these studies demonstrated that stratifying on relevant clinical characteristics, i.e., onset of asthma in childhood or adulthood, increased power to detect novel loci that are both shared between these groups as well as specific to age of onset, and provided novel insights into shared and distinct mechanisms in the etiology of asthma with onset in childhood and adulthood.

GWAS of Moderate-to-Severe Asthma

The underlying reasons for why certain patients develop severe asthma while the majority of patients with asthma respond to modest interventions continues to be an important, unanswered question. Earlier studies of severe or difficult-to-treat asthma[34] and moderate-to-severe asthma[35] identified associations with known asthma loci, but no new asthma loci were identified. Shrine, Portelli, John *et al*[6] recently reported the largest GWAS of moderate-to-severe asthma using a two-stage case-control design. In the first stage, a discovery GWAS was conducted in 5,135 moderate-to-severe asthma cases from three UK cohorts, including the UK Biobank. This was followed by analysis of the associated loci in a separate cohort of 5,414 moderate-to-severe asthma cases.

Twenty-one independent loci were genome-wide significant in stage 1 and an additional 11 loci were considered suggestive significant ($P < 1x10^{-6}$). These 32 loci were carried forward to stage 2, where 25 independent loci were replicated. Twenty-two loci were previously associated with asthma, including three independent associations at the HLA locus. The ORs in the meta-analysis were relatively modest, with the largest OR = 1.21 at both the *HLA-DQB1* locus on chromosome 6p21.32 and the *IL33* locus on chromosome 9p24.1. All significant loci other than the *MUC5AC* locus on chromosome 11p15.5 were associated with asthma in a previous large GWAS of self-reported doctor diagnosed asthma[31] and were considered to be shared between mild and moderate-to-severe asthma. The *MUC5AC* locus was considered to possibly be specific to severe asthma. Subsequent studies of gene expression revealed that an associated variant at the *MUC5AC* locus (rs11603634) was associated with expression of *MUC5AC* in bronchial

304 epithelial cells, with increased expression of this gene associated with the asthma risk allele.
305 Moreover, *MUC5AC* expression was higher in bronchial epithelial cells from subjects with
306 severe asthma compared to cells from non-asthmatic controls.

307 Overall, this study suggests that the genetic risk is largely shared between moderate-to-
308 severe asthma and mild asthma. Variants near *MUC5AC* were suggested to be specific to
309 moderate-to-severe asthma because it was not reported in a previous large GWAS. However, the
310 recent study by Pividori, Schoettler *et al*[4] reported associations with variants at this locus to be
311 associated with adult onset asthma. In fact, this was one of very few loci that had a smaller *P*-
312 value and larger odds ratio in the adult onset asthma GWAS compared to the childhood onset
313 GWAS. Taken together, these combined results suggest that variants near *MUC5AC* may
314 contribute to the generally more severe presentation in adult onset asthma.

315

316 GWASs of Asthma Drug Response

317 Inhaled corticosteroids are the cornerstone of asthma management and are highly effective in
318 controlling asthma symptoms in most patients. While previous GWASs identified more than 15
319 loci associated with inhaled corticosteroid responsiveness in mostly European populations[36-43],
320 two groups recently focused on this phenotype in non-European populations. Hernandez-
321 Pacheco *et al*[44] conducted a meta-analysis of asthma exacerbations using 1,347 admixed children
322 with asthma while being treated with inhaled corticosteroids. No genome-wide significant loci
323 were identified, but a locus near *APOBEC3B* and *APOBEC3C* on chromosome 22q13.1 was
324 suggestively significant and replicated in a meta-analysis of studies conducted on Europeans[44].
325 In the second study, Levin, Gui *et al* assessed corticosteroid responsiveness in 244 African

American subjects 12 years of age and older who were monitored while on inhaled corticosteroid therapy[45]. Two variants surpassed the genome-wide significant threshold. One variant, rs3827907, on chromosome 14q11.2 was associated with exacerbations in three of four independent cohorts (African Americans in the Study of Asthma Phenotypes and Pharmacogenetic Interactions by Race-Ethnicity [SAPPHIRE] and Study of African Americans, Genes and Environment [SAGE] II and Latino subjects in GALA II), validating their effect on asthma control. The associated allele at this variant was also associated with lower expression of *RNASE2* and lower eosinophilic inflammation in blood from African Americans[44].

Bronchodilators are used for immediate relief of asthma symptoms due to their effects on smooth muscle relaxation and decreased airflow obstruction, and bronchodilator responsiveness is variable and differs between ethnic groups[46]. Genetic associations with bronchodilator responsiveness were previously identified[47-50] but African American subjects were underrepresented in these studies, despite their having higher than average asthma morbidity and mortality[25-28]. A genome-wide association and admixture mapping of bronchodilator responsiveness in 2,779 African Americans was recently reported. Spear *et al* [51] identified a single variant, rs73650726, on chromosome 9q21.32 that was associated with decreased airflow obstruction after inhalation of albuterol, a bronchodilator. The allele associated with bronchodilator responsiveness was very rare in non-African ancestry populations. Variants in high LD with the lead variant were located in enhancer histone marks in lung tissue, suggesting that this is a region important in regulating the expression of a distant gene. A second locus on chromosome 10q21.1 was associated with bronchodilator responsiveness in the combined African-American and Latino analysis, with the associated variants located in *PRKG1*. The lead variant, rs7903366, was also associated with expression of this gene in lung tissue[52].

In a second study of bronchodilator responsiveness, Mak, White, Eckalbar, Szpiech *et al*[53] included subjects from three admixed populations: Puerto Ricans, Mexicans and African Americans. As part of the NHLBI TOPMED (Trans-Omics for Precision MEDicine) program, they performed whole genome sequencing of 1,441 asthma subjects at the tails of the distributions of FEV_1 responses to albuterol. A trans-ethnic meta-analysis revealed a genome-wide significant region near *LINCO1194* and *DNAH5* on chromosome 5p15.2, and eight other regions that were of suggestive significance ($P < 7.06 \times 10^{-6}$). Two of the five regions were significant only in Mexicans and one region was significant only in African Americans; none of the regions were significant in Puerto Ricans.

Collectively, GWASs of corticosteroid and bronchodilator responsiveness in non-European admixed populations highlighted both trans-ethnic and ancestry-specific genetic loci contributing to drug response. Notably, none of the associated loci overlap with loci associated with asthma *per se*, indicating that different mechanistic pathways underlie risk for asthma inception and response to asthma therapeutics.

GWAS of Asthma Remission

The trajectory of asthma symptoms is highly variable, with many individuals diagnosed with asthma in childhood undergoing remission. Remission rates are higher in children diagnosed with asthma than in adults diagnosed with asthma[54, 55]. Vonk *et al* performed GWASs of clinical remission and complete remission of asthma in 178 and 55 subjects, respectively, after a median follow-up of 15.5 years among a cohort of 790 asthma cases[56]. No loci in either GWAS were genome-wide significant, likely due to the small number of cases and limited power to detect

associations. However, three variants among the 25 most significant independent variants from both GWASs replicated in two cohorts (n=81 and 54 with clinical remission; n=7 and 14 with complete remission), which required the same direction of effect and a 1-sided $P < 0.05$ in both GWAS). These three variants were also associated with the expression in lung tissue of genes at each locus (i.e., in *cis*), highlighting three genes, *POL1* in clinical remission and *FRS2*/*CCT2* and *IL1RL1*/*IL18R* in complete remission, as potentially associated with remission. Future larger studies are needed to confirm these associations and to identify additional variants relevant to clinical remission.

GWAS of Asthma and Allergic Diseases

Clinical observations, epidemiologic studies and GWAS[13, 20, 57, 58] have suggested shared etiologies between asthma and allergic diseases, particularly for childhood onset asthma[4, 5]. Zhu *et al*[22] recently published a study on the shared genetic architecture between asthma and allergic diseases (hay fever/allergic rhinitis and eczema/atopic dermatitis) using UK Biobank data. They first showed significant genetic correlations between 26,685 cases with allergic disease ± doctor diagnosed asthma and 14,085 cases with doctor diagnosed asthma, using a shared set of 76,768 controls (all European ancestry). In contrast, correlations between asthma and three non-allergic immune-mediated diseases (rheumatoid arthritis, Crohn's disease, and ulcerative colitis, also from the UK Biobank) were not significant, demonstrating specificity of the genetic correlation between asthma and allergic disease.

They performed two separate GWAS, one for allergic disease ± asthma and one for doctor diagnosed asthma. In the primary analyses the GWASs revealed 33 loci associated with

allergic diseases and 32 loci associated with asthma at genome-wide levels of significance. Most were at loci previously reported for these traits, although they report discovery of eight novel allergic disease loci and six novel asthma loci. Variants at six loci were significant in both GWASs and 22 additional loci harbored significant (but different) variants in each GWAS. Thus, overall 28 loci showed genome-wide significant evidence of associations with both allergic disease ± asthma and with asthma.

To more rigorously assess genetic correlations between phenotypes and to improve power, they performed a cross-trait analysis using the same set of controls[59]. This analysis indicated that most loci are significant for both traits, identifying 38 independent loci that contributed to both allergic disease ± asthma and asthma. This included many known asthma and allergy loci, such as those in the *HLA-DQ* region, which included the most significant cross-trait associations, and *C11orf30*, *IL1R1*, *SMAD3*, *TLR1*, *IL7R*, *GATA3*, and *FLG*, among others. Most of the loci considered to be novel in this study were subsequently reported in the studies of childhood and adult onset asthma, also using UK Biobank data[4, 5]. The cross-trait correlations were replicated in a European ancestry cohort, GABRIEL[17], and in the multi-ancestry Early Genetics and Lifecourse Epidemiology (EAGLE) cohort[60]. Most of the same loci were also associated with both traits, at least at suggestive levels of significance ($P < 1.5 \times 10^{-7}$).

The 38 significant loci were most enriched for increased expression in skin, followed by esophagus, vagina, lung and whole blood, highlighting the importance of epithelial cells (skin, esophagus and vagina), immune cells (blood), and an important target organ (lung). These results are similar to those reported for genes at childhood onset asthma loci (skin and blood) and adult onset asthma loci (lung and blood)[4], likely reflecting the inclusion of both childhood onset and adult onset asthma cases in this study.

Although overlapping genetic architecture between asthma and allergic diseases is not surprising, the inclusion of individuals with asthma among the allergic disease cases may have increased the evidence for correlations between traits and for some of the loci. The relatively small number of genome-wide significant loci discovered in this study compared to those in the GWASs of childhood onset and adult onset asthma in the UK Biobank[4, 5] may be due to combining cases with varying ages of onset[5]. Nonetheless, this comprehensive analysis of the shared genetic architecture of asthma and allergic diseases identified many candidate pathways and mechanisms for the observed co-occurrences of these diseases in the same individuals. Future studies will be needed to address whether shared variants regulate the same genes and whether shared genes are regulated by the same genetic variants, and why perturbations of these genes or pathways lead to only allergic disease, only asthma, or both in different individuals.

GWASs of Allergic Rhinitis

Allergic rhinitis is the most prevalent atopic disease, with a strong genetic component, as evidenced by heritability estimates over 0.65[61-63]. In 2018, Waage *et al*[21] reported the largest GWAS of allergic rhinitis and identified 41 risk loci, including 20 loci that had not previously been related to the disease. This study was a meta-analysis of 18 independent studies of European ancestry, including more than 59,000 cases and 152,000 controls in a discovery phase, followed by replication of 25 novel loci in a second set of 10 independent studies comprised of more than 60,000 cases and 618,000 controls. The loci selected for replication included 16 that were genome-wide significant and 9 that were suggestively significant (p-values between $5x10^{-8}$ and $1x10^{-6}$ based on a gene set enrichment with focus on immunological signaling). The novel

loci mainly included genes with annotated functions in innate and adaptive immune response processes, such as toll-like receptor signaling, natural killer cell formation, components of the high affinity IgE receptor and the NF-kappaB complex, antigen-induced B and T cell development and V(D)J receptor recombination, B cell migration and interaction of T and B cells with the lymphatic system. Many of the previously known risk loci that were reported in this study, such as the HLA-DQ, *IL13*, *IL21/IL2*, *C11orf30*, *IL1R1*, *SMAD3*, *TLR1*, and *GATA3* loci, have been associated with a broad spectrum of immune-mediated diseases, including allergic diseases (e.g., asthma, atopic dermatitis) and autoimmune/inflammatory diseases (e.g., psoriasis, type 1 diabetes, Crohn's disease). Although replicated within European ancestry populations, none of the novel loci replicated in non-European cohorts (n = ~6,000 cases). Nonetheless, the observation of overlapping genetic risk for immune-mediated diseases is consistent with results of previous studies showing shared risk loci between asthma and allergic diseases[20, 22] and between asthma and autoimmune diseases[64, 65]. Functional consequences were suggested for the majority of the 41 risk loci based on informatics inferences. In particular, regulatory effects for many loci were supported by publicly available data on eQTLs, methylation QTLs, and enhancer-promoter interactions. In addition, 17 associated variants were predicted to lead to amino acid changes in encoded proteins, including predicted deleterious changes in the genes *NUSAP1*, *SULT1A1* and *PLCL*, using the Variant Effect Predictor database[66] and SIFT[67].

The most associated loci were within the HLA region on chromosome 6q21. In order to better characterize the number of independent associations at this immunological important locus, the investigators performed conditional analyses and observed not only associations with a number of classical HLA alleles, such as *HLADQB1*02:02*, *HLA DQB1*03:01*, *HLA*-

461 *DRB1*04:01*, and *HLAC*04:01*, but also with specific amino acid variants. Most interestingly,
462 the two most strongly associated amino acids within the class I and class II regions were HLA-B
463 Asp116/His116-/Leu116 and HLA-DQB1 His30, respectively. These changes were all within the
464 peptide-binding pockets and predicted to modify the antigen binding properties of these HLA
465 molecules. The investigators also conducted GWASs of allergic sensitization to inhaled allergens
466 (defined as the presence of allergen-specific IgE) and of non-allergic rhinitis (defined as rhinitis
467 without evidence for allergic sensitization) in order to identify overlapping or specific disease
468 mechanisms between these phenotypes and allergic rhinitis. The most significant loci reported in
469 these GWAS largely overlapped with allergic rhinitis.

470 Fujii *et al* [68] performed a two-stage case-control GWAS on any, cedar-specific and
471 cypress-specific pollinosis, another term for allergic rhinitis. In the genome-wide discovery stage
472 they analyzed 311, 229, and 134 cases, respectively, and attempted replication in a cohort of 270
473 cases[68]. The studies failed to discover any genome-wide significant results, likely due to the
474 small number of cases, using trait definitions based on self-administered questionnaires, and lack
475 of information on cedar- and cypress-specific pollinosis in the replication cohort.

476

477 GWAS of Food Allergies

478 Although genetic factors have been implicated in the etiology of food allergies, genetic
479 dissection of this complex phenotype is hampered by extensive heterogeneity resulting from the
480 large variety of food allergens, misclassification of due to inappropriate assessment methods
481 (oral food challenge versus specific IgE measurement/skin prick test versus patient's self-
482 report), and the transient nature of some food allergies early in life. Moreover, there is a

considerable variability in the prevalence of food allergy between ethnicities, geographical regions, and to different food allergens. More than 170 foods have been reported to cause IgE-mediated reactions[69], which can be life-threatening, and genes associated with food allergy risk can be specific to single foods or shared between different food allergies or even between food allergies and other allergic diseases, such as atopic dermatitis and asthma. Four studies published within the time period covered by this review reported results of 14GWAS on food allergy. All of these studies were relatively small (all fewer than 5,000 subjects), and identified few (0-2) genome-wide significant loci.

The first GWAS of allergy to hydrolyzed wheat protein, defined as an immediate-type I allergic reaction after use of hydrolyzed wheat protein-containing facial soaps or consumption of wheat products, was performed in a primary cohort of 452 and a replication cohort of 45 female Japanese cases[70]. Despite the small number of cases, the study identified two loci meeting genome-wide levels of significance: one in the *HLA-DQA1* region on chromosome 6p21 and one in the *RBFOX1* region on chromosome 16p13. Notably, the most significant SNP at the *HLA-DQA1* (class II) locus, rs9271588, corresponded to the HLA-DQA1 amino acid variant Glu34, suggesting genetic effects on peptide binding and antigen presentation, analogous to the associations with amino acid variants reported by Waage *et al*[21] in a GWAS of allergic rhinitis, described above, and to earlier studies of allergen-specific HLA associations[8-10, 12].

Three additional studies performed GWAS of a range of food allergies. One, performed in the Chicago Food Allergy Study cohort[71], was comprised of 588 European ancestry child-parent trios with one index offspring affected by any food allergy (defined as self-reported allergic reaction to peanut, egg, cow's milk, soy, wheat, walnut, fish, shellfish, and/or sesame seed in combination with detection of specific IgE and/or a positive skin prick test). In this study,

Liu *et al* considered two alternative models. The first considered maternal genetics effects on the child's risk for food allergy, presumably due to the intrauterine environment but not to the direct transmission of risk alleles, and the second considered parent of origin effects, in which the associations in the child varied depending on whether the risk allele was inherited from the mother or the father. Each model was evaluated in GWASs for any food (n = 501), peanut (n = 301), egg white (n = 201), or cow's milk (n = 275) allergy. In only one of the eight GWASs performed, only one variant at a locus on chromosome 4q31.3 reached genome-wide significance ($P < 5x10^{-8}$), with less significant support at this locus for association with individual foods. This association, however, was not supported by evidence from nearby SNPs. The associated SNP was located in a noncoding RNA (*LOC101927947*) with unknown function. Additional analyses stratified by the affected offspring's sex did not yield significant associations.

A second study by Khor *et al* examined food allergy for seven different foods in two Japanese female cohorts recruited as part of an industry-initiated women's healthcare program ("Luna Luna family"). Both cohorts were comprised of between 252 and 563 cases (depending on the specific food allergy, based on self-reported allergic food reactions[72]). Two loci reached genome-wide significance, one in the shrimp allergy GWAS and one in the peach allergy GWAS, both with SNPs in the HLA-DR/DQ gene region. The investigators then used SNP genotypes to impute HLA types and showed that the *HLA-DRB1*04:05-HLA-DQB1*04:01* and *HLA-DRB1*09:01-HLA-DQB1*03:03* haplotypes were associated with shrimp and peach allergy, respectively ($P_{(shrimp)} = 3.92\times10^{-19}$, and $P_{(peach)} = 1.15\times10^{-7}$). A third study by Asai *et al* identified one risk locus for peanut allergy and one for any food allergy using a two-stage analysis that first performed a GWAS in 850 peanut allergy cases from the Canadian Peanut Allergy Registry (CanPAR; defined by history of an allergic reaction against peanut in

combination with a positive skin prick test and/or specific IgE), and then conducted a meta-analysis of CanPAR plus six independent studies providing a total of 1,582 and 7,267 cases for peanut allergy and general food allergy, respectively[73, 74]. Both the GWAS and meta-analysis of peanut allergy identified an association with variants at the *HLA-DQB1* locus. The associated variants were independent of the known asthma GWAS SNPs and the association remained significant in an analysis stratified by asthma. This finding supports the notion that the HLA-associated risk alleles for peanut allergy are independent of the HLA-associated risk alleles for asthma. Both the food allergy GWAS and meta-analysis identified a risk locus on chromosome 11q15.3, near the *C11orf30* and *LRRC32* genes, which is a well-established genetic risk locus for other atopic or inflammatory barrier diseases, such as atopic dermatitis, asthma, and inflammatory bowel disease.

Taken together with the Waage *et al* study on allergic rhinitis (described above)[21], these results provide evidence for a strong role of HLA class genes in conferring risk for allergic diseases. Importantly, they further support the suggestion that HLA-associated risk for allergic disease is distinct from the HLA-associated risk for asthma[11]. Combined results from GWAS of asthma and allergic diseases suggest that the latter is potentially mediated by genetic effects on antigen presentation, while the former is potentially mediated by genetic effects on gene expression, a hypothesis that could be evaluated in future studies. The studies from the past 18 months further suggest that while the HLA region is of general importance for allergic diseases, HLA alleles may play an especially important role in food allergies, with high specificity to distinct foods and food allergens.

GWAS of Atopic Dermatitis

No GWASs for atopic dermatitis were published within the short time interval covered by this review. The largest and most recent GWAS was published by Paternoster, Standl *et al* in 2015[60]. This was a multi-ethnic meta-analysis of 26 studies comprised of 21,399 cases and 95,464 controls. They discovered 10 novel susceptibility loci for atopic dermatitis and comprehensively discussed the 21 known risk loci reported in seven previous GWASs. The detection of 23 genome-significant loci in a sample of 21,399 ethnically diverse atopic dermatitis cases is consistent with the data shown in **Figure 1**, but the larger number of genome-wide significant loci in the GWAS compared to similarly sized samples of European adult onset asthma cases (n=17 loci) and multi-ethnic asthma cases (n=18 loci), potentially suggests a stronger genetic component to atopic dermatitis.

Conclusions

The studies reviewed here both support and challenge the notion that "bigger is better". Clearly, the availability of very large data sets such as the UK Biobank[4-6, 22] and large meta-analyses[13, 21] have significantly advanced our knowledge of the genetic architecture of asthma and allergic diseases in European ancestry populations. These studies have further demonstrated that early onset asthma has a stronger genetic component and higher heritability than onset of asthma in adulthood, with more than 2.5-times the number of genome-wide significant loci associated with the former compared to the latter, despite at least double the sample sizes for the latter compared to the former[4, 5]. Similarly, a relatively small study of asthma patients selected to have moderate-to-severe disease[6] revealed more associated loci than larger studies of "asthma" in more

heterogeneous populations[13, 14]. Finally, studies of highly specific food allergies (i.e., hydrolyzed wheat protein[70], shrimp[72], peach[72], peanut[73]) in relatively small samples provided genome-wide significant associations with variants in the class II HLA region. The trade-off between larger sample sizes to increase power and focus on specific subtypes to decrease clinical heterogeneity has been referred to as a Faustian bargain[75], which the studies reviewed here have illustrated. As such, "bigger is not necessarily better" if heterogenous phenotypes with different genetic architectures are combined, thereby reducing the ability to detect loci associated with specific subtypes of asthma.

However, while asthma and allergic disease genetic studies in European ancestry populations have made significant progress, studies in racial and ethnic groups that carry the greatest burden of asthma and allergic disease remain significantly underrepresented among GWAS[76]. Although the past 18 months have witnessed increased numbers of GWAS in non-European populations, they have not been sufficiently powered to detect genetic differences that underlie these disparities or to validate associations that have been discovered in European ancestry populations[2, 3, 13, 14]. Due to the greater genetic heterogeneity inherent in admixed populations, GWASs in African Americans and Latino/Hispanic populations may require even greater sample sizes to achieve equivalent power to studies in European populations. We anticipate that many of the loci identified in GWASs of childhood and adult onset asthma, moderate-to-severe asthma, asthma-allergic disease overlaps, and allergic rhinitis will be relevant across ethnicities, and that both novel loci and greater frequencies of known risk alleles will underlie some of the disparities in disease burden. We look forward to future larger studies in these populations that allow stratification by sub-phenotypes and directly address these important outstanding questions.

The ultimate goal of GWASs and of genomic medicine is to translate knowledge from newly identified variants to the clinic for prediction, diagnosis and management. The use of individual polygenic risk scores to identify individuals at risk and of whole genome sequencing in patients with rare/extreme forms of allergic disease seem realistically achievable in the near-future, at least in European populations. However, the clinical utility of polygenic risk scores for asthma and common allergic diseases do not translate across ethnic racial groups and will require additional work to achieve this goal. Moreover, the utility of polygenic risk scores to delineate disease subtypes and understand molecular mechanisms has not yet been proven. Many whole genome sequencing studies are underway in both large cohorts and smaller but more homogenous and deeply phenotyped individuals, and the value of these studies should be revealed over the next few years. Newer approaches, such as reverse phenotyping of individuals using genetic markers to define endotypes[77], and integrating of multi-omics measures using machine learning and other advance computational tools, are already becoming standard. Finally, there is still the need for fine-mapping studies at associated loci to pinpoint causal variants and the genes they regulate, as well as functional validation studies that link the effects of genetic risk and disease mechanisms to disease, which have been done so far for surprisingly few asthma and allergic disease loci.

615 Table 1. Chromosomal locations of 28 loci associated with asthma or allergy in at least 5 GWASs of asthma or at least two GWASs
616 of an allergic disease conducted during the period covered by this review. The genes listed are those reported in each study for the
617 association. Rows are sorted by number of associations with asthma and then number of GWASs (in parentheses). Regions correspond
618 to those shown in **Figure 2**. *Number includes multiple independent associations at the same locus (number of GWASs reporting at
619 least one significant association in that region).

Chromosomal region	Number of associations with asthma*	Number of associations with allergy	Genes	References
6p21.3	28 (10)	6 (5)	*HLA-DQB1, HLA-DRB1, HLA-DRB6, HLA-DQA1, HLA-DPA1, HLA-B, HLA-C, MICA, MICB, COL11A1, TCP11, SCUBE3, HLA-DOB, HCP5, MCCD1*	Asai, Eslami et al[73], Dahlin, Sordillo et al[14], Demenais et al[13], Ferreira et al[5], Khor et al[72], Noguchi, Akiyama, Yagami et al[70], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
10p14	15 (7)	3 (2)	*GATA3, CELF2, SFTA1P, loc101928272, RP11*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
2q12.1	13 (7)	2 (2)	*IL1R1, IL1RL1, IL1RL2, IL18R1, IL18RAP, MIR4772, SLC9A2, SLC9A4*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
5q22.1	12 (7)	3 (2)	*CAMK4, WDR36, SLC25A46, TMEM232, TSLP*	Dahlin, Sordillo et al[14], Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
5q31.1	11 (9)	1 (1)	*C5orf56, SLC22A5, IRF1, KIF3A, IL4, CCNI2, IL13, RAD50, SEPT8*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
9p24.1	11 (8)	3 (2)	*RANBP6, IL33, KIAA2026, MIR4665, TPD52L3, GLDC, UHRF2*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Zhu et al[22]
17q12-21	11 (7)	1 (1)	*ORMDL3, GSDMB, ZPBP2, ERBB2, MED1, CSF3, ERBB2, GRB7, GSDMA, GSDMB, IKZF3, LRRC3C, MED24, MIEN1, MIR4728, MIR6884, PGAP3, PNMT, PSMD3, SNORD124, STARD3, TCAP*	Daya et al, Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]

11q13.5	10 (7)	3 (3)	*LRRC32*, *C11orf30*, *EMSY*, *THAP12*, *WNT11*, *PRKRIR*	Asai, Eslami et al[73], Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
15q22.33	10 (6)	1 (1)	*SMAD3*, *SMAD6*, *AAGAB*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
16p13.13	7 (7)	2 (2)	*CLEC16A*, *DEXI*, *CIITA*, *RMI2*, *SOCS1*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21], Zhu et al[22]
2q37.3	7 (6)	1 (1)	*D2HGDH*, *ING5*, *GAL3ST2*	Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Zhu et al[22]
8q21.13	7 (6)	1 (1)	*MIR5708*, *TPD52*, *ZBTB10*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Waage, Standl et al[21]
12q13.2	7 (5)	1 (1)	*TESPA1*, *MUCL1*, *NEUROD4*, *RAB5B*, *CDK2*, *SUOX*, *RPS26*, *ERBB3*, *IKZF4*, *PA2G4*, *RAB5B*, *RPL41*, *ZC3H10*	Ferreira et al[5], Pividori, Schoettler et al[4], Zhu et al[22]
1q21.3	7 (3)	2 (1)	*C1orf68*, *CRCT1*, *CRNN*, *FLG*, *FLG2*, *HRNR*, *LCE2A*, *LCE2B*, *LCE2C*, *LCE2D*, *LCE3A*, *LCE3B*, *LCE3C*, *LCE3D*, *LCE3E*, *LCE4A*, *LCE5A*, *NBPF18P*, *RPTN*, *S100A11*, *TCHH*, *TCHHL1*, *CLEC16A*, *TDRKH*, *RORC*	Ferreira et al[5], Pividori, Schoettler et al[4], Zhu et al[22]
6p22.1	7 (3)	0	*DDX6*, *CXCR5*, *TRIM26*, *TRIM15*, *TRIM39*, *GPX5*, *TRIM27*	Ferreira et al[5], Pividori, Schoettler et al[4]
6q15	6 (6)	1 (1)	*BACH2*, *MAP3K7*, *GJA10*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Shrine, Portelli, John et al[6], Waage, Standl et al[21]
17q21.2	6 (5)	1 (1)	*KRT24*,*KRT222*,*SM ARCE1*, *STAT5B*, *GHDC*, *STAT5A*	Pividori, Schoettler et al[4], Ferreira et al[5], Zhu et al[22]
4q27	5 (4)	2 (2)	*IL2*, *IL21*, *ADAD1*, *KIAA1109*	Ferreira et al[5], Shrine, Portelli, John et al[6], Waage, Standl et al, Zhu et al
17q21.32	5 (4)	0	*ZNF652*,*TBX21*, *TBKBP1*, *OSBPL7*, *PHB*	Ferreira et al[5], Shrine, Portelli, John et al[6], Pividori, Schoettler et al[4]
18q21.33	5 (3)	0	*TNFRSF11A*, *KIAA1468*, *ZCCHC2*, *SERPINB7*, *SERPINB11*, *SERPINB2*	Ferreira et al[5], Pividori, Schoettler et al[4]

15q22.2	4 (4)	1 (1)	*RORA, ANXA2, VPS13C, NARG2*	Demenais et al[13], Ferreira et al[5], Pividori, Schoettler et al[4], Waage, Standl et al[21]
19q13.11	4 (3)	2 (2)	*CEBPA, SLC7A10, LRP3*	Ferreira et al[5], Waage, Standl et al[21], Zhu et al[22]
10p15.1	4 (3)	1 (1)	*PRKCQ, PFKFB3, SFMBT2, IL2RA, RBM17*	Ferreira et al[5], Pividori, Schoettler et al[4], Zhu et al[22]
4p14	3 (3)	4 (2)	*FAM114A1, MIR574, TLR1, TLR6, TLR10, KLF4*	Ferreira et al[5], Pividori, Schoettler et al[4], Waage, Standl et al[21], Zhu et al[22]
12q24.31	3 (3)	2 (1)	*SPPL3, HNF1A, PITPNM2, CDK2AP1, C12orf65, SPPL3, ACADS*	Pividori, Schoettler et al[4], Waage, Standl et al[21]
2p25.1	3 (3)	2 (2)	*LINC00299, ID2, RNF144A*	Ferreira et al[5], Pividori, Schoettler et al[4], Waage, Standl et al[21], Zhu et al[22]
1q24.2	3 (2)	1 (1)	*CD247*	Ferreira et al[5], Shrine, Portelli, John et al[6], Zhu et al[22]
15q15.1	1 (1)	2 (2)	*ITPAK, CHP1, EXD1, INO80, NDUFAF1, NUSAP1, OIP5, RTF1*	Ferreira et al[5], Waage, Standl et al[21], Zhu et al[22]
20q13.2	1 (1)	2 (2)	*LOC101927770, ZNF217, NFATC2, KCNG1, TSHZ2*	Ferreira et al[5], Waage, Standl et al[21], Zhu et al[22]
5p13.2	1 (1)	2 (2)	*CAPSL, IL7R, LOC100506406, SPEF2, UGT3A1*	Ferreira et al[5], Waage, Standl et al[21], Zhu et al[22]

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838 Figure Legends

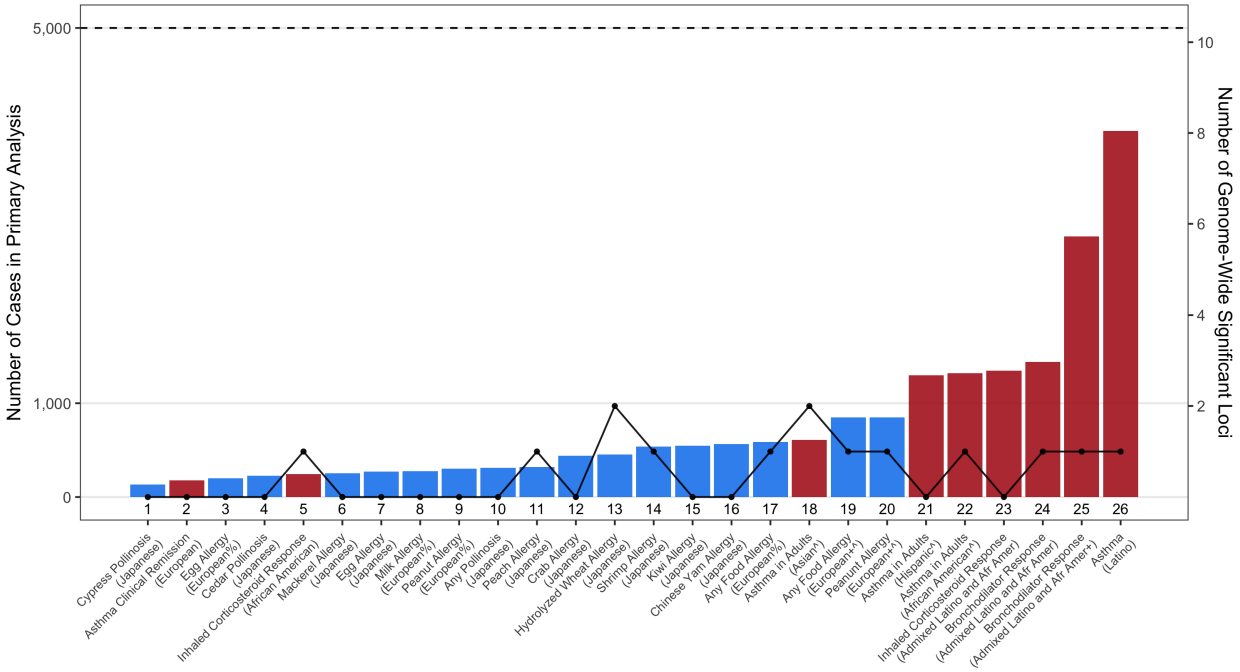
839 **Figure 1**. Published GWASs between January 1, 2018 and June 30, 2019 on asthma (red bars)
840 and allergic diseases (blue bars), separated into those with less than 5,000 cases (A) and those
841 with more than 5,000 cases (B). Each bar corresponds to a study, described on the x-axis legend.
842 The number of cases included in the primary analysis is shown on the left y-axis and the number
843 of genome-wide significant loci is shown on the right y-axis. The dashed horizontal line
844 indicates studies with 5,000 cases or more (above the dashed line) or fewer than 5,000 cases
845 (below the dashed line). Note that the y-axis differs between A and B.

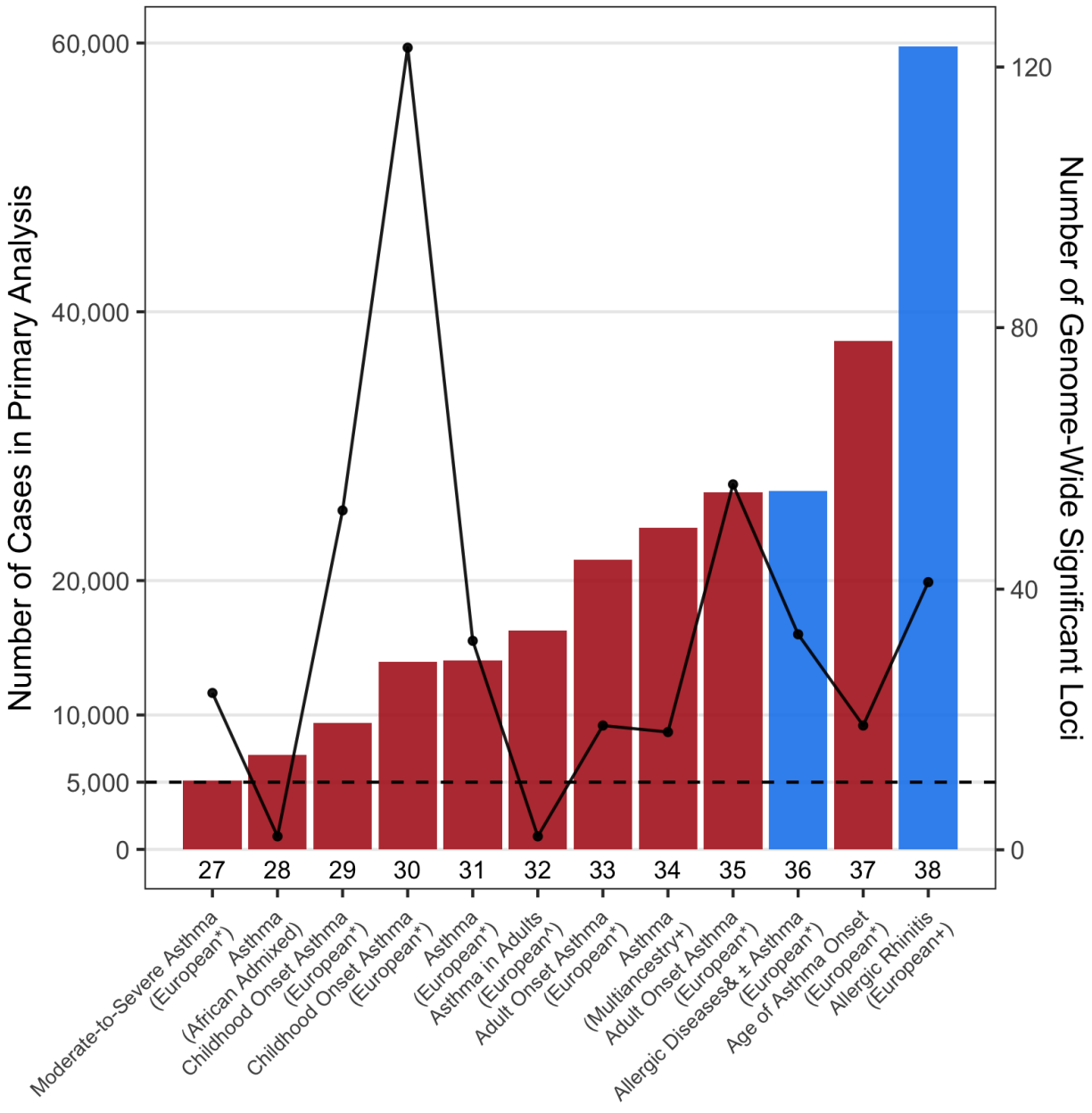
846 1, Fujii et al.[68]; 2, Vonk et al.[56]; 3, Liu et al.[71]; 4, Fujii et al.[68]; 5, Levin, Gui et al.[45]; 6-7, Khor et
847 al.[72]; 8-9, Liu et al.[71]; 10, Fujii et al.[68]; 11-12, Khor et al.[72]; 13, Noguchi, Akiyama, Yagami et
848 al.[70]; 14-16, Khor et al.[72]; 17, Liu et al.[71]; 18, Dahlin, Sordillo et al.[14]; 19-20, Asai, Eslami et
849 al.[73]; 21-22, Dahlin, Sordillo et al.[14]; 23, Hernandez-Pacheco et al.[44]; 24, Mak, White, Eckalbar,
850 Szpiech et al.[53]; 25, Spear et al.[51]; 26, Gignoux, Torgerson et al.[3]; 27, Shrine, Portelli, John et
851 al.[6]; 28, Daya et al.[2]; 29, Pividori, Schoettler, et al.[4]; 30, Ferreira et al.[5]; 31, Zhu et al[22]. 32,
852 Dahlin, Sordillo et al.[14]; 33, Pividori, Schoettler et al.[4]; 34, Demenais et al.[13]; 35, Ferreira et al.[5];
853 36, Zhu et al.[22]; 37, Pividori, Schoettler et al. [4]; 38, Waage et al.[21]

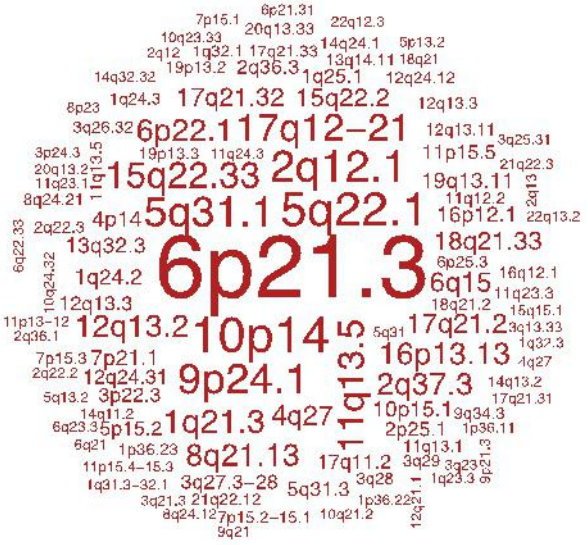
854 [^]GERA (Kaiser Permanente Northern California Genetic Epidemiology Research in Adult
855 Health and Aging Cohort); [+]Results from meta-analysis; [#]Analysis performed by admixture
856 mapping; [%]Study conducted in trios; [&]Allergic rhinitis/hay fever and/or atopic
857 dermatitis/eczema; [*]Study includes case and controls from the UK Biobank.

858

Figure 2. Word cloud of genome-wide significant loci in asthma and allergic diseases from the studies described in Figure 1. The size of the type is proportional to the number of times the locus was reported as genome-wide significant. Independent associations at the same locus (e.g., HLA) are each counted. In the published studies reviewed here, loci reported as 17q12, 17q21 and 17q12-21 were combined as 17q12-21 and loci reported at the HLA region (6p21.31, 6p21.32 and 6p21.33) were grouped as 6p21.3. Loci on the X chromosome that were reported in only some studies were not included. The genes reported in each study are shown in Table 1.




Number of Cases in Primary Analysis
60,000
40,000
20,000
10,000
5,000
0
Number of Genome-Wide Significant Loci
120
80
40
0
27
28
29
30
31
32
33
34
35
36
37
38
Moderate-to-Severe Asthma (European*)
Asthma (African Admixed)
Childhood Onset Asthma (European*)
Childhood Onset Asthma (European*)
Asthma (European*)
Asthma in Adults (European^)
Adult Onset Asthma (European*)
Asthma (Multiancestry+)
Adult Onset Asthma (European*)
Allergic Diseases& ± Asthma (European*)
Age of Asthma Onset (European*)
Allergic Rhinitis (European+)


Asthma
6p21.31
7p15.1
20q13.33
22q12.3
10q23.33
2q12
1q32.1
17q21.33
14q24.1
5p13.2
19p13.2
2q36.3
13q14.11
18q21
14q32.32
1q25.1
12q24.12
8p23
1q24.3
17q21.32
15q22.2
12q13.3
3q26.32
6p22.1
17q12–21
12q13.11
3q25.31
3p24.3
19p13.3
11q24.3
11p15.5
21q22.3
20q13.2
15q22.33
2q12.1
19q13.11
11q23.1
8q24.21
11q12.2
5q31.1
5q22.1
16p12.1
22q13.2
2q22.3
4p14
13q32.3
18q21.33
6p21.3
6p25.3
1q24.2
16q12.1
6q15
10q24.32
12q13.3
11q23.3
18q21.2
15q15.1
11p13–12
12q13.2
10p14
17q21.2
3q13.33
2q36.1
5q31
16p13.13
1q32.3
7p15.3
7p21.1
4q27
2q22.2
12q24.31
9p24.1
2q37.3
14q13.2
5q13.2
3p22.3
17q21.31
14q11.2
10p15.1
9q34.3
6q23.3
5p15.2
1q21.3
4q27
2p25.1
1p36.11
6q21
1p36.23
11q13.1
8q21.13
17q11.2
3q29
3q23
11p15.4–15.3
1q23.3
9p21.3
1q31.3–32.1
3q27.3–28
5q31.3
3q28
3q21.3
21q22.12
1p36.22
12q21.1
8q24.12
7p15.2–15.1
10q21.2
9q21
Allergic Disease
9q34.2
8q21.13
7p15.1
1p22.1
17q12–21
13q14.11
12q24.12
2q37.3
11q23.3
1p36.11
12q24.31
15q22.2
14q21.1
5q22.1
12q13.2
19q13.11
10q24.32
8q24.21
12q13.3
3p21.2
15q22.33
4p14
1q21.3
6q15
2q12.1
6p21.3
10p15.1
4q24
5p13.2
2q31.1
4q27
11q23.1
10p14
15q15.1
1p31.1
1q24.2
11q13.5
1q23.3
20q13.33
9p24.1
2q36.3
5q31.1
14q24.1
16p13.13
2p25.1
17q21.2
2p23.2
20q13.2
16p13
3q28
16p11.2
1p36.23
2q33.1