



Asthma genomics and pharmacogenomics

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In this review, we summarize recent published work interrogating the relationship between genetic variation or gene expression regulation across the genome and asthma or asthma treatment outcomes. This includes 11 genome-wide association studies of asthma phenotypes that collectively identified 64 novel loci; transcriptome-wide asthma association studies which identified genes involved in virus recognition, bacterial infection, lung tissue remodeling, eosinophilic and neutrophilic inflammation and genes in the chromosome 17q12 asthma susceptibility locus; and three epigenome-wide studies of asthma that had robust sample sizes and replicated findings. We also highlight pharmacogenomic studies of corticosteroids, bronchodilator response to albuterol and zileuton, although finding from these studies may still be preliminary due to their relatively small sample sizes and limited availability of replication cohorts.

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Introduction

Asthma is a complex disease where both genes and the environment contribute to disease susceptibility and pathogenesis. Variability in inter-individual therapeutic responses to commonly used asthma medications suggest that genetic variation may also affect treatment outcomes. Unbiased genome-wide, hypothesis-free study designs can lead to discoveries useful for understanding underlying biology, predicting risk and improving treatment. The purpose of this review is to highlight and summarize recent published work interrogating the relationship between genetic variation or gene expression regulation across the genome and asthma or asthma treatment

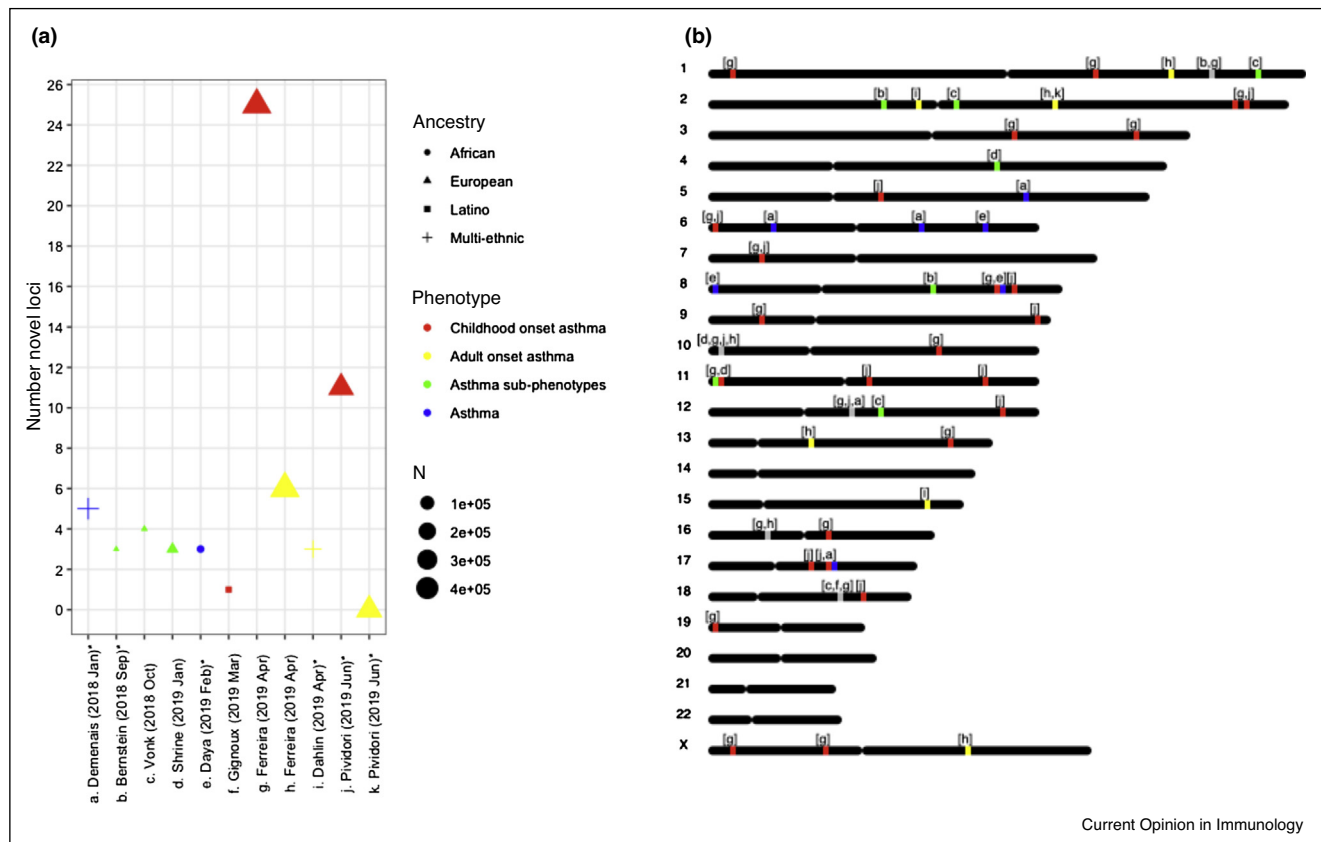
outcomes. We review publications from December 2017 to December 2019 that performed genome-wide association studies (GWAS), transcriptome wide studies (TWAS) and epigenome-wide studies (EWAS).

Recent discoveries of asthma risk loci from GWAS

The risk for developing asthma is imparted by genetic variants through the cumulative effects of many different gene regions or loci, which may interact with multiple potential environmental exposures to cause asthma, a complex genetic disease. Similar to other complex diseases, early asthma genetic studies used family-based designs to identify regions of the genome that are co-inherited with disease outcomes, and after the mapping of the human genome, genetic variants in specific, biologic candidate genes were tested for association with asthma and related phenotypes. Over the past decade, much of the insights on genetic risk for asthma were gleaned from GWAS. During the review period, 11 GWAS of asthma phenotypes were published. Collectively, 64 novel loci were identified by these GWAS (Figure 1).

At the beginning of the review period, the Trans-National Asthma Genetic Consortium (TAGC) published a large meta-analysis combining GWAS from 65 asthma studies [1•]. The multi-ethnic TAGC GWAS more than doubled the size of asthma GWAS (23,948 asthmatics + 118,358 non-asthmatic controls) and represent the largest GWAS of asthma conducted in asthma research cohorts. The TAGC GWAS identified five loci not previously reported by asthma GWAS. Although multi-ethnic, ancestry representation in the TAGC GWAS reflect the over-representation of European ancestry in GWAS in general [2] (89.7% of subjects of European ancestry, only 5.8%, 3.7% and 0.9% of African, Japanese and Latino ancestry, respectively). Subsequent to TAGC, two studies of asthma conducted in non-European ancestry populations were reported. The Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) published a large GWAS of asthma in African ancestry populations (7009 asthmatics and 7645 non-asthmatics) [3]. The CAAPA GWAS identified two novel loci and provided strong replication evidence for four of the 18 genome-wide significant TAGC loci. Gignoux *et al.* performed a genome-wide interrogation for risk of asthma in Latinos using admixture mapping, where the ancestral origin of chromosomal segments across the genome is tested for association, rather than genetic variants [4•]. This analysis identified a locus on chromosome 18q21, and subsequent fine-mapping implicated the *SMAD2* gene, a co-factor in the Transforming Growth

Figure 1



Summary of the number of novel findings reported by asthma GWAS published 1 December 2017–31 December 2019.

(a) The number of novel loci reported by asthma GWAS, not reported by any prior published GWAS of asthma. Studies are ordered by publication date. Studies without evidence for replication are denoted by *. **(b)** The location of loci reported by GWAS summarized in panel (a). The bracketed alphabetic characters correspond to the studies listed on the x-axis of panel (a). Loci colors correspond to the GWAS phenotype definition in panel (a), but with grey denoting loci reported by GWAS of more than one phenotype.

Factor- β (TGF- β) signaling pathway known to play a role in asthma biology.

Three GWAS of asthma subphenotypes were published during the review period [5–7]. Shrine *et al.* published a large GWAS of moderate-to-severe asthma (N = 30,810) and reported three novel loci, including the *MUC5AC* gene, whose gene product contributes to airway mucin production [6]. Two GWAS of relatively small sample size, one of asthma remission [7] (N = 790) and another of diisocyanate-induced asthma [5] (N = 329), reported a handful of novel loci for these respective asthma severity phenotypes. While GWAS of smaller sample size are prone to false discoveries and need to be independently confirmed, both studies were complimented by omic studies demonstrating that the identified variants regulate the expression of biologically plausible genes.

A number of studies used large scale genetic databases tied to health questionnaires and/or electronic health

records to investigate genetic risk for childhood versus adult onset asthma [8*,9**] and adult-onset asthma [10] risk (N ranging between 68,623–460,158). GERA performed a multi-ethnic GWAS of asthma in older adults and reported four novel asthma risk loci (three from GWAS in Asian ancestry subjects and one from GWAS in African Americans) [10]. Two GWAS used data from the UK Biobank to investigate differences in genetic risk factors for childhood versus adult onset asthma [8*,9**]. Collectively, the two studies identified 39 novel asthma loci. Both studies reported a larger number of loci associated with childhood-onset asthma compared to adult-onset asthma, despite a ~2 fold smaller number of individuals with childhood-onset asthma. Taken together with higher SNP-based heritability (heritability attributable to GWAS array variants) for childhood asthma compared to adult-onset asthma estimated by both these studies, these findings support a larger role for genetic variation determining risk of childhood-onset asthma compared to asthma in adults. Atopic dermatitis in

children is a major risk factor for development of childhood onset asthma, and interestingly, the analyses by Pividori *et al.* highlighted the role of variants in the *FLG* gene and genes controlling epithelial barrier function as a risk factor for childhood-onset asthma [9**].

Asthma regulatory variation from transcriptome and epigenome-wide studies

As is the case with other complex diseases, most asthma GWAS discoveries implicate regulatory variation in non-coding regions rather than protein coding changes in exons, suggesting that at a genetic level, regulation of RNA and, ultimately, protein levels, are important for disease pathogenesis. TWAS and EWAS are two study designs that interrogate gene expression regulation at a genome-wide level, which capture the effects of both genetic and environmental risk factors for disease. TWAS directly measure gene expression through RNA sequencing or gene-RNA expression assays, and in EWAS the regulation of gene expression is investigated by testing for association between the proportion of DNA methylation (5-methyl-cytosine versus unmethylated cytosine) at a specific cytosine (CpG) locus within CpG islands or CpG-rich regions and the phenotype of interest. In addition to TWAS and EWAS, gene expression and DNA methylation data are useful resources for interpreting GWAS findings, but have been limited due to availability of the tissue types necessary to evaluate gene regulation in airway cells. Many of the asthma GWAS discussed in the previous sections leveraged gene expression or methylation data from a smaller subgroup of their own study subjects [4*,5] or external data sets [1**,3,6,7,8*,9**,10] to examine biological mechanisms of associations, as well as assessing enrichment of genetic risk variants that regulate expression in particular pathways or tissues.

A number of recent studies measured expression in tissues highly relevant to asthma pathogenesis in cohorts enriched for severe asthma: surgically removed lung tissue from deceased individuals [11], Bronchoalveolar Lavage (BAL) cells [12,13], and sputum [13–15]. These studies identified signatures of differentially expressed genes involved in virus recognition [11], bacterial infection [13], lung tissue remodeling [11,12], eosinophilic inflammation [12,14], the highly replicated chromosome 17q12 asthma susceptibility locus [12], and neutrophilic inflammation [13–15]. Two of these studies noted signatures of medication use — cAMP signaling influenced by beta-agonist exposure [12] and steroid-insensitive IL-17 responses [13]. With the aim of identifying potential therapeutic pathways to target severe, adult-onset asthma, Hekking *et al.* compared 105 transcriptome gene sets related to asthma, ICS treatment response, leukocyte lineage, and induced lung injury between severe adult-onset asthmatics and childhood-onset asthmatics in sputum, nasal brushings and endobronchial brushings. This gene set variation analysis found an enrichment of gene

signatures associated with downregulation during inhaled fluticasone treatment, eosinophilia, the presence of mast cells, and group 3 innate lymphoid cell involvement in adult-onset severe asthma [16]. Another study investigated transcriptional profiles of asthma exacerbations in a pediatric asthma cohort recruited to evaluate acute viral respiratory infections, and identified two distinct molecular phenotypes, representing up and downregulation of interferon (IFN)-gamma, with downregulation of IFN-gamma associated with increased frequency and severity of asthma exacerbations [17].

Transcriptomic studies offer the opportunity to identify changes in gene expression profiles with exposure to external stimuli, and was used to identify a set of genes expressed in airway epithelia and involved in mucociliary clearance that differentiated asthmatics from controls upon exposure to nanoparticle aerosols [18], and to show that TGF- β mediated differentiation of fibroblasts to myofibroblasts underlie changes in airway remodeling in asthma [19]. A number of studies leveraged existing asthma transcriptomic datasets to generate hypotheses related to asthma pathophysiology: (1) suppressed epithelial differentiation in asthma [20], (2) overexpression of small non-coding RNAs involved in the initiation of DNA replication in asthmatics [21], (3) differences in gene regulatory variation with asthma risk specific to males and females [22], and (4) an enrichment of airway epithelial cell regulatory variants in the TAGC asthma GWAS [23]. Newly emergent single-cell sequencing technologies now make it possible to examine higher-resolution expression profiles at the individual cellular level, and has been used by to identify novel gene expression signatures in asthma versus unaffected airway cells, including novel mucous ciliated cell states that increase mucin-producing cells, and a shift from airway structural to Th2-dominated cell communication [24**]. Insights from the relatively few other single-cell sequencing studies relevant to asthma has recently been reviewed by Barret and Shalek [25].

Many of the EWAS reported during the review period were conducted in children [26*,27**,28,29,30,31,32,33,34,35**,36,37,38], including prospective studies [28–31,33,35**]. Asthma-related phenotypes include asthma [26*,27**,32,33,35**,36–40], total serum IgE (tIgE) [30,31], atopy [29,35**,38], asthma and COPD [41], wheezing [28,36] and air pollutants [34], and some EWAS investigated the relationship between environmental exposures, changes in methylation and asthma [32,33,37,39–41]. Two studies demonstrated a correlation between epigenetic age inferred from DNA methylation and risk for asthma and allergies [31,38]. We also note the value of correlating findings from DNA methylation with transcriptomics, to confirm the effect of methylation on RNA expression of specific genes, which was done in eight of the 16 studies [26*,27**,34,35**,36,38,39,41].

Similar to transcriptomic studies, disease-relevant tissue types are an important consideration in EWAS. Tissue types used in recent EWAS include blood [26*,27**,29–31,33,34,36,37,40], saliva [28], lung [39,41], and nasal epithelium [32,35**,38].

Although DNA methylation from whole blood capture immune system function and is thus relevant to asthma, recent studies of IgE-mediated allergic disease demonstrated that eosinophil counts are the strongest factor influencing methylation differences [42–44], which may overpower methylation differences not driven by eosinophilia. Lung and lower airway tissue are arguably better target tissues than blood for asthma studies but require more invasive procedures (bronchoscopy) to collect. For this reason, a number of asthma researchers have opted to collect nasal epithelial brushings for transcriptomic and methylation studies. Nasal epithelium transcriptomes are strongly correlated with bronchial transcriptomes, are altered in asthmatics, distinguish sub-phenotypes of disease (Th2-high versus Th2-low, atopic asthma), and demonstrate altered expression of asthma GWAS genes in asthma cases versus controls [45–47]. Furthermore, nasal epithelium asthma EWAS have detected effect sizes ~10 times larger than asthma EWAS in blood [46]. Consequently, smaller sample sizes are required for nasal epithelium asthma EWAS. The most notable EWAS of asthma susceptibility published during the review period were two asthma EWAS in peripheral blood cells [26*,27**], and one nasal epithelium EWAS [35**], all performed in children. These EWAS had robust sample sizes and replicated their findings. The peripheral blood study by Xu *et al.* (discovery N = 1548) revealed novel associations related to methylation of the *DICR1* (plays a role in microRNA production), *STX3* (plays a role in maintaining epithelial barrier function), *LIPIN1* (regulates mast cell degranulation and the anaphylactic response) and *MBL2* (plays a role in sphingolipid transport) genes [26*]. The differentially methylated CpG islands and regions identified by another peripheral blood EWAS (discovery N = 6434) implicated several genes that are targets of approved drugs (24 unique approved drugs across all differentially methylated results) [27**]. A nasal epithelium asthma EWAS by Forno *et al.* (discovery N = 483) identified genes involved in epithelial barrier function, airway epithelial integrity and immune regulation [35**]. Furthermore, classification models of atopy and atopic asthma based on methylation signatures from nasal epithelium identified in this EWAS performed well in the discovery and replication cohorts (AUC ranging between 0.74 and 1) [35**].

Pharmacogenomic studies identify novel loci for therapeutic responsiveness

In pharmacogenetic studies, genetic variants or polymorphisms are associated with pharmacodynamic endpoints such as lung function change, asthma exacerbations and

symptom control during treatment with a specific drug. Before this review period, many asthma pharmacogenetic studies have focused on candidate genes within the biologic pathways associated with therapeutic response phenotypes during treatment with glucocorticoid, beta agonist, and leukotriene modifier therapies [48]. Because GWAS require large cohorts, as well as multiple cohorts to independently replicate initial discoveries, only a small number of pharmacogenomic studies, where the entire genome is interrogated for association with endpoints, were reported before this review for glucocorticoids, beta agonists, and leukotriene modifiers, reviewed elsewhere [48–52].

Six recent pharmacogenomic studies reported findings relevant to response to corticosteroids; three GWAS [53*,54*,55**], two EWAS [56,57] and one TWAS [58]. The study by Hawcutt *et al.* performed a GWAS to identify genetic variation that may play a role in adrenal suppression, an adverse effect of corticosteroid therapy. Although their study was small (N = 499), variants at a gene encoding a platelet-derived growth factor protein (*PDGFD*) was associated with this adverse outcome and was replicated in an independent cohort (N = 159) [55**]. *PDGFD* is a plausible candidate gene, as it is highly expressed in the adrenal gland, and is a class of protein required for steroid production in cells. Levin *et al.* performed a SNP-by-inhaled corticosteroid (ICS) genome-wide interaction study to identify genetic variants that modify asthma control response outcomes in 244 African Americans [53*]. This study identified a variant associated with ICS treatment outcomes in the presence of eosinophilic inflammation; the variant was also associated with lower expression of an eosinophil-derived neurotoxin gene, *RNASE2*. In addition to this biologically plausible mechanism, the finding replicated in independent African American (N = 1366) and Latino (N = 405) asthma cohorts. Hernandez-Pacheco *et al.* performed a GWAS of asthma exacerbations in Puerto Rican and African American children treated with ICS, and identified a locus intergenic between *APOBEC3B* and *APOBEC3C*, which was replicated in a previous GWAS database of European ancestry populations [54*]. *APOBEC3B* and *APOBEC3C* are expressed in lung tissues and encode APOBEC3 proteins that play a role in the innate immune response to viral infections which is a risk factor for asthma exacerbations in children.

The Childhood Asthma Management Program (CAMP) performed an EWAS of ICS response as measured by change in lung function (forced expiratory volume) after 8 weeks of treatment initiation, and identified an association between the methylation of the *BOLA2* gene, a gene that is upregulated in lung tissues in the context of respiratory syncytial virus infection [56]. A second study leveraged CAMP to perform a discovery EWAS of ICS response as measured by the absence or presence of

exacerbations requiring emergency department visits, hospitalizations, and oral corticosteroid use during ICS use [57]. The same response outcome measure was available in the Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE) study and the Genetic Epidemiology of Asthma in Costa Rica Study (GACRS) for replication, and was followed by meta-analysis of associations nominally associated in each cohort. These analyses replicated associations between hypomethylation of the *IL12B* gene and absence of emergency department visits or hospitalizations, and hypermethylation of the *CORT* gene was associated with the absence of oral corticosteroid. *IL12B* plays a role in Th2 induced airway hyperresponsiveness, and mouse models have shown that *CORT* regulates inflammatory cytokine and chemokine production. Kan *et al.* investigated changes in transcriptomic signatures in response to glucocorticoid exposure in airway smooth muscle cells from donors with fatal asthma (N = 9) as well as non-asthmatic donors (N = 7) [58]. Enriched gene pathway expression between smooth muscle cells between fatal asthma versus controls included chemokine receptor binding and guanylate cyclase in the nitric oxide pathway. Interestingly, their study did not find differential gene expression signatures when comparing glucocorticoid response in fatal asthma compared to no asthma, although larger sample sizes are needed to confirm this finding and the control comparison group was controls, and not those with milder asthma.

Two GWAS of bronchodilator response to albuterol (a short-acting β_2 -adrenergic receptor agonist) were published during the review period. The study by Mak *et al.* [59] investigated response to albuterol in three admixed populations (African American, Mexican American and Puerto Rican children, N = 1441), maximizing power to detect associations by selecting study participants from the tails of the albuterol response distribution (i.e. the very high and very low responders). Common variants near the *DNAH5* gene, which has previously been reported as associated with lung function, was significantly associated with albuterol bronchodilator response. Another unique characteristic of the study is the use of whole-genome sequence data, allowing the study authors to also investigate the role of rare genetic variants in response to albuterol. Rare genetic variation contributed to the identification of a locus between the *ADAMTS3* and *COX18* genes, which has previously been reported as associated with beta-adrenergic responses in cardiovascular trait murine models. Mak *et al.* were not able to replicate their findings in independent cohorts, noting racial/ethnic underrepresentation in asthma research studies, and that this lack of replication may suggest that their findings are racial/ethnic specific. The GWAS by Spear *et al.* investigated response to albuterol in the same study cohorts using a GWAS genotyping array, including all participants rather than those from the tails of the albuterol response distribution; discovery (N = 2779)

[60]. This GWAS identified three SNPs intronic to the *PRKG1* gene, a highly plausible candidate gene that plays a role in the nitric oxide signaling pathway, which in turn modulates vasodilation in response to beta-agonists [60]. However, similar to Mak *et al.*, these findings did not replicate in independent cohorts, again underscoring the need to increase racial diversity in asthma genetic research studies.

The combination of ICS and long-acting beta agonist (LABA) therapy is often used to treat moderate-to-severe asthma. To better understand the biological mechanism of improved outcomes with this combined therapy, Rider *et al.* investigated the interaction between ICS and LABA using a transcriptomic study in bronchial airway epithelial cells [61]. Their study showed that glucocorticoid-induced gene transcription is enhanced twofold to threefold by LABA; however, this was not due to glucocorticoid receptor binding, and their findings suggested that LABAs enhance effects of specific, rather than all, glucocorticoid-inducible genes. In identifying some of these gene-specific effects, their study is an important proof of concept for applying transcriptomic pharmacogenomics to discover glucocorticoid receptor ligands most beneficial for combination therapy with LABA.

One study investigated response to leukotriene modifiers, specifically zileuton [62]. The study authors derived lymphoblastoid cell lines from asthmatics, treated the cells with zileuton or ethanol (as control), measured LTB₄ (where high measures correspond to a poor response) and gene expression, and then used GWAS array data to catalog genetic variants associated with LTB₄ (protein quantitative trait loci [pQTL]) and gene expression (expression QTL or eQTL) changes in response to zileuton treatment. Pathway analyses of pQTLs, eQTLs and variants from a previous GWAS [50] demonstrated an enrichment of genes in the PI3K phosphatidylinositol signaling pathway. Further functional validation confirmed that the PI3K pathway, which plays a role in pro-inflammatory lipid signaling, was activated in poor responder lymphoblastoid cells.

Conclusion

In part due to much larger sample sizes available through the emergence of large-scale biobanks, recent GWAS of asthma has substantially increased the catalog of genetic variation associated with asthma risk, severity, and therapeutic outcomes and have improved the characterization of the genetic architecture of asthma. Unfortunately, much of this catalog and categorization are mainly derived from European ancestry cohorts, but the growth of multi-ethnic biobanks integrating clinical outcome and genome-wide datasets may soon remedy disparity [63]. Phenotypes derived from EHR and questionnaires are based on self-report or physicians' diagnosis which is less objective than in traditional research cohorts where more

detailed phenotypic characterizations can confirm a diagnosis of asthma and inform with respect to important asthma endotypes. However, the large, well-powered sample sizes available in biobanks largely overcome this limitation by confirming known asthma loci while identifying novel loci which have replicated. Despite these successes, much of the heritability of asthma has yet to be explained and could relate to uncharacterized gene-by-environment interactions, epigenomic or transcriptomic variation in non-coding regions, and ancestry-specific rare or low frequency variants which cumulatively could impact asthma phenotypes. The continued implementation of multi-omic approaches in racially diverse asthma cohorts, including clinical trials with more refined, longitudinal phenotypes and pharmacogenetic outcomes, will be critical to further characterize the genomic architecture of asthma. In these research settings, over the past 2 years, larger genome-wide multi-omic approaches such as TWAS and EWAS are becoming a reality. The future challenge of integrating data from GWAS, TWAS and EWAS will require systems biology approaches [64], an exciting avenue to facilitate future discoveries.

Conflict of interest statement

Dr. Ortega reports personal fees from Sanofi, outside the submitted work.

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