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The Genetics and Genomics of Asthma

Saffron A.G. Willis-Owen, William O.C. Cookson, and Miriam F. Moffatt

National Heart and Lung Institute, Imperial College London, London SW7 2AZ, United Kingdom; email: s.willis-owen@imperial.ac.uk, w.cookson@imperial.ac.uk, m.moffatt@imperial.ac.uk

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Abstract

Asthma is a common, clinically heterogeneous disease with strong evidence of heritability. Progress in defining the genetic underpinnings of asthma, however, has been slow and hampered by issues of inconsistency. Recent advances in the tools available for analysis—assaying transcription, sequence variation, and epigenetic marks on a genome-wide scale—have substantially altered this landscape. Applications of such approaches are consistent with heterogeneity at the level of causation and specify patterns of commonality with a wide range of alternative disease traits. Looking beyond the individual as the unit of study, advances in technology have also fostered comprehensive analysis of the human microbiome and its varied roles in health and disease. In this article, we consider the implications of these technological advances for our current understanding of the genetics and genomics of asthma.

INTRODUCTION

Asthma is a chronic disease of the airways defined by its symptoms, which include reversible airflow obstruction, inflammation, and bronchial hyperresponsiveness. The ancient Egyptians, Greeks, and Romans made reference to the symptoms of asthma, and today the disease is estimated to affect 235–334 million people worldwide (44, 53).

Asthma is heterogeneous in both its clinical presentation and its prognosis. The International Classification of Diseases diagnostic system primarily groups asthma patients according to the severity and persistence of symptoms and the presence of complications (152). Statistical approaches to subtype asthma likewise observe substructure among symptoms (such as atopic status, wheeze, and cough) (67), but the nature of this structure may depend on choices relating to variable inclusion and methodology (34), limiting the overall clinical application of such phenotype-driven techniques.

Asthma has a substantial genetic component, with estimates of heritability ranging from 35% to 95% (116). As such, the genomic era brought with it hopes of molecular subtyping and associated personalization of treatment plans for the disease, as has been seen in the case of breast cancer (20, 28). However, given that the heritability of asthma is incomplete (<1), environmental factors must also account for a fraction of the phenotypic variance. Consistent with this, epidemiological studies have identified a range of pre-, peri-, and postnatal environmental factors, including mode of delivery, diet, and early lower respiratory tract infection, that confer relative risk or protection. Attempts to map the genetic architecture of asthma have identified a broad spectrum of potential contributory genes. Many of these genes demonstrate inconsistent patterns of replication between cohorts, most likely reflecting a combination of true positive and true negative results and the unseen hand of gene × environment and gene × gene interaction. Nevertheless, a handful of genes have shown robust association with asthma. While these effects individually account for only a minority of phenotypic variance, they provide novel insights into the underlying pathogenic processes as well as potential sources of interaction with the environment. Here, we review the genetic and genomic factors that are currently implicated in the pathobiology of asthma and consider the ability of these factors to differentiate between patient groups.

GENETIC LINKAGE AND POSITIONAL CLONING

Prior to the advent of high-throughput technologies, the cost of genotyping was substantial. As such, genome-wide, hypothesis-free approaches were limited to relatively small panels of informative (multiallelic) markers distributed approximately evenly across the genome. Genotype at these sites was determined in families with multiple affected individuals, allowing identification of contiguous regions that showed co-transmission with the trait of interest. Broad loci specified as harboring susceptibility variants could then be explored at a higher resolution through positional cloning or positional candidate gene studies, ideally identifying genes or the individual sequence variants responsible. This technique, highly successful in the arena of Mendelian traits, was the mainstay of early genetic studies of asthma, with more than 25 such studies reported between 1996 and 2006 (reviewed in 18, 35). While these studies led to the identification of only eight genes, *ADAM33*, *DPP10*, *PHF11*, *NPSR1*, *HLA-G*, *CYFIP2*, *IRAK3*, and *OPN3* (3, 11, 78, 112, 114, 142, 151, 162), that putatively contribute to the genetic etiology of the disease, each of small effect, all but one were novel, with no previously suspected role in asthma.

The eight positionally cloned putative susceptibility genes (listed in **Table 1**) are diverse in their described functions, ranging from cytokine and chemokine processing (*DPP10*) (3) to class-switch recombination (*PHF11*) and airway remodeling (*ADAM33*). *ADAM33* was the first gene

Table 1 Positionally cloned putative asthma genes and their signals in genome-wide association studies

Positionally cloned gene	Region	Description	Mapped traits accompanied by low *p* values
ADAM33 (ADAM metallopeptidase domain 33) (142)	20p13	Metalloprotease	None
DPP10 (dipeptidyl peptidase–like 10) (3)	2q14	Serine protease	Severe influenza A (H1N1) infection (51), response to antidepressants in depression (83), survival in microsatellite instability low/stable colorectal cancer (154), gut microbiome composition (winter) (30), subjective well-being (117), systolic blood pressure in sickle cell anemia (15), bipolar disorder (71), obesity-related traits (25), response to paliperidone in schizophrenia (negative Marder score) (82), and suicide attempts in major depressive disorder (50)
PHF11 (PHD finger protein 11) (162)	13q14	Double-stranded DNA–binding protein	Breastfeeding duration (24) and cardiac hypertrophy (119)
NPSR1 (neuropeptide S receptor 1) (78)	7p14	G-protein-coupled receptor	IgG glycosylation (81), postbronchodilator FEV1 (94), and postbronchodilator FEV1/FVC ratio (94)
HLA-G (major histocompatibility complex, class I, G) (112)	6p21	Major histocompatibility complex antigen	Autism spectrum disorder or schizophrenia (10), eosinophil percentage of granulocytes (9), eosinophil percentage of white cells (9), neutrophil percentage of granulocytes (9), Crohn's disease (75), lung adenocarcinoma (103), IgE levels (57), and childhood ear infection (123)
CYFIP2 (cytoplasmic FMR1-interacting protein 2) (114)	5q33	G-protein modulator	Lung function (FEV1/FVC) (144) and IgG glycosylation (81)
IRAK3 (interleukin 1 receptor–associated kinase 3) (11)	12q14	Kinase	Smooth-surface caries (160)
OPN3 (opsin 3) (151)	1qter	G-protein-coupled receptor	Daytime sleep phenotypes (134)

This table summarizes the genes positionally cloned for asthma per se and includes their genomic location. The publicly available GWAS Catalog (19) was systematically queried for these genes, and traits accompanied by a p value $\leq 5 \times 10^{-6}$ at the time of writing are listed. Abbreviations: FEV1, forced expiratory volume measured during the first second of forced breath; FVC, forced vital capacity.

to be positionally cloned for asthma. Its transcripts show a preferential distribution in cells of mesenchymal origin (139, 142), and its sequence variants associate not only with asthma per se but also with bronchial hyperresponsiveness, early-life lung function, lung function decline across the life course, and chronic obstructive pulmonary disease (31), consistent with the gene's proposed role in airway remodeling.

Unfortunately, as with many other so-called complex (or multifactorial) traits, positionally cloned putative asthma susceptibility genes have been hampered by issues of inconsistent replication. While there are a host of competing explanations for this phenomenon, contributory factors may include false positives, allelic heterogeneity, natural variation in linkage disequilibrium between causative and genotyped sequence variants among assayed populations, the effects of other genetic variants and environments, and/or gene × gene or gene × environment interactions. By way of example, in 2003 *PHF11* was posited to be responsible for the chromosome 13q14 linkage peak that influences asthma and total serum immunoglobulin E (IgE) levels, as variants within this gene demonstrated the strongest evidence of association with the tested traits (162). Consistent with this hypothesis, *PHF11* was also shown to accelerate class-switch recombination to IgE in

murine activated B cells (68). Although the chromosomal interval that contains *PHF11* has been implicated in asthma, atopy, and IgE traits in several linkage studies and the association between *PHF11* and asthma has been independently replicated, replication has not been successful across the full range of populations tested (101). Within the genome, *PHF11* is positioned in a linkage disequilibrium block that includes both *PHF11* and its immediate physical neighbor, *SETDB2* (SET domain bifurcated 2). These two genes, separated by an interval of just 4 kb, are transcribed in the same direction and form fusion transcripts in some tissues (162). A recent analysis of this region identified a functional variant located within the 5′ untranslated region of *SETDB2* that is capable of regulating the transcription of *SETDB2* and shows significant association with total serum IgE (66). Such situations are difficult to disentangle but highlight the potential for differing linkage disequilibrium patterns and/or allelic heterogeneity to manifest as inconsistent replication.

CANDIDATE GENES

The prohibitively high cost of genotyping combined with the paucity of available markers in the pre-genome era rendered high-resolution, hypothesis-free approaches impractical. As such, the vast majority of high-resolution studies were limited to individual genes whose candidacy was suggested by alternative, converging lines of evidence, including positional, mechanistic, and/or theoretical data. By design, this approach precluded identifying truly novel components of disease pathobiology, although it did instead provide a tool to ratify or refute existing candidates. The cost efficacy of the approach resulted in a large increase in the number of candidate gene association studies. However, these studies were invariably carried out in small, low-powered cohorts that are also prone to false positives, and consequently many of the results failed to replicate consistently between populations. This phenomenon is not limited to the context of asthma, but is widely recognized across a broad spectrum of complex traits (64, 69). For example, in 2002 a cross-trait analysis of candidate gene associations showed that less than 4% of associations studied three or more times were consistently replicated (64).

The design of genetic association studies is relatively simplistic. For categorical traits like disease status, allele frequencies at a small set of variants positioned in and around a gene of interest or the combinations thereof (haplotypes) are compared between cases and controls. These variants can take any format, such as insertion–deletion (indel) polymorphisms or single-nucleotide polymorphisms (SNPs). As of 2006, prior to publication of the first asthma genome-wide association study (GWAS), candidate gene studies had implicated more than 100 genes in the etiology of asthma (115). Of these, fewer than 10% had been replicated in more than 10 studies, even when the phenotype definition was expanded to include both asthma and atopy phenotypes and when the gene was considered the unit of replication, rather than individual variants or combinations thereof (115).

These relatively more promising asthma candidate genes included the prototypical type 2 cytokine genes *IL4* (interleukin 4) and *IL13* (interleukin 13) and the IL4 receptor gene *IL4RA* (now known as *IL4R*). Additionally, implicated in more than 10 studies was the beta-2 adrenergic receptor gene *ADRB2*, the candidacy of which has been supported by the efficacy of beta agonists in asthma and the gene's influence on beta-agonist responsiveness (100), and the positional candidate *ADAM33*. Other frequently replicated genes included the gene encoding the beta subunit of the high-affinity IgE receptor (*FCER1B*, now known as *MS4A2*), the proinflammatory cytokine gene *TNFA*, the surface antigen gene *CD14*, and the major histocompatibility locus genes *HLA-DRB1* and *HLA-DQB1*. That said, experimentally, some candidate genes have received considerably more attention than others, and factors such as publication bias, which influences the number of

negative replications reported in the literature, further confound the direct interpretation of results. Unfortunately, large-scale meta-analyses capable of providing a clear synthesis of all available data are few and far between, not least owing to the diversity of the populations and environments studied. Furthermore, those that do exist often fail to detect a consistent overall effect, casting doubt on the credibility of many targets identified during the candidate gene era.

GENOME-WIDE ASSOCIATION STUDIES

GWASs leverage the high frequency of SNPs across the genome, as defined through sequencing, to enable the application of allelic association on a genome-wide scale. This technique is founded on the common disease–common variant principle, which predicts that the genetic architecture of common diseases is in large part composed of common, low-penetrance variants. Since GWASs are agnostic to what part(s) of the genome might be associated, they enable the detection of previously undescribed and unsuspected genetic components, assuming they are present in the population at an appreciable frequency. Variants detected as significantly associated in a GWAS are not necessarily themselves pathogenic, but may be in linkage disequilibrium with other, perhaps rarer, untyped variants that may be the source of the association.

The first GWAS of asthma was carried out in 2007 (109), and today, according to the publicly available GWAS Catalog (19), 38 loci, or genomic regions, have been associated with asthma per se at a *p*-value threshold of $p < 5 \times 10^{-8}$, the standard threshold commonly applied in GWASs (**Table 2**). This number markedly increases if intermediate phenotypes and disease subtypes are additionally considered. Among these 38 asthma-associated loci, the most consistently replicated, through GWAS and non-GWAS positional candidate gene studies and across a diverse range of ethnic backgrounds, is the cluster of genes on chromosome 17q12–21. This locus, originally brought to light in the first GWAS of asthma in 2007 (109), harbors sequence variants capable of regulating the expression level of several physically colocalized genes. These genes include *ORMDL3* (orosomucoid-like 3) (58, 90, 109), *GSDMB* (gasdermin B) (58), and *GSDMA* (gasdermin A) (60, 90). Variants that are capable of regulating the expression of local genes are referred to as *cis*-acting expression quantitative trait loci (eQTLs), and at least in the case of *ORMDL3*, they appear to have cell type–specific effects (89).

Large-scale studies powered to identify subgroup effects have further shown that the 17q12–21 signal is specific to childhood-onset disease. In addition, the relationship between genotype and disease appears to be moderated by early environmental exposures, including tobacco smoke (17), respiratory infection (130), and place of residence (132). The pathogenic mechanism or mechanisms that mediate these effects are as yet unclear. At least two of the genes positioned within the bounds of the asthma-associated 17q12–21 locus, however, appear to participate in similar processes underlying airway remodeling and responsiveness in asthma. Functional studies in mice show that *ORMDL3* expression affects airway remodeling (107), including airway smooth-muscle proliferation and contractility (21), with airway remodeling preceding airway inflammation. Similarly, transgenic mouse studies of *GSDMB* also suggest roles in airway remodeling and responsiveness but in the absence of lung inflammation (29). *ORMDL3*, an endoplasmic reticulum gene, mediates sphingolipid homeostasis and the unfolded protein (stress) response, while the function of *GSDMB* (also known as *GSDML*) is largely undescribed. In addition, there is growing evidence that expression of *ORMDL3* (or its mouse counterpart, *Ormdl3*) in the lung influences the host response to fungal (*Alternaria*) challenge (92) as well as the antiviral response to rhinovirus infection—showing a significant relationship with both viral load and the extent of airway inflammation (131). These data therefore suggest a mechanism for the interaction between genotype at the 17q12–21 locus and early respiratory infection in the development of asthma (130).

Table 2 Loci implicated in the etiology of asthma via genome-wide association studies with a p value $< 5 \times 10^{-8}$

Region	Reported gene(s)	Reference(s)
1p36.22	*PEX14*	123
1q21.3	*IL6R*	45
1q23.1	*PYHIN1*	137
1q23.3	*B4GALT3*, *ADAMTS4*	123
1q24.2	*CD247*	123
1q25.1	*TNFSF18*, *TNFSF4*	123
1q31.3	*DENND1B*, *CRB1*	129
1q32.1	*ADORA1*	123
2p25.1	*ID2*	123
2q12	*IL18R1*, *IL1RL1*, *IL1RL2*	108, 123, 124, 137
2q37.3	*D2HGDH*	123
3q28	*LPP*	123
4p14	*TLR1*	123
4q31.21	*LOC729675*	63
5q12.1	*PDE4D*	62
5q22.1	*SLC25A46*, *TSLP*	63, 123, 137
5q31	*RAD50*, *NDFIP1*	123
6p21.31	*GRM4*, *HGMA1*	4
6p21.32	*PBX2*, *NOTCH4*, *C6orf10*, *BTNL2*, *HLA-DRA*, *HLA-DRB5*, *HLA-DQA1*, *HLA-DQ*, *HLA-DQB1*, *HLA-DQA2*, *HLA-DOA*, *HLA-DPB1*	63, 80, 108, 113, 123, 124
6p21.33	*HLA-C*, *MICA*	123
6q15	*BACH2*	123
7q22.3	*CDHR3*	123
8q21.13	*TPD52*, *ZBTB10*	123
8q24.11	*SLC30A8*	113
9p21.2	*EQTN*, *TEK*, *MOB3B*	4
9p24.1	*RANBP6*, *IL33*	108, 123, 137
9q34.11	*PTGES*	4
10p14	*LOC338591*, *GATA3*	63, 123
10q21.3	*JMJD1C*	4
11q13.5	*C11orf30*, *LRRC32*	45, 123
12q13.2	*CDK2*, *IKZF4*	63
12q13.3	*STAT6*, *LRP1*	123
14q24.1	*RAD51B*	123
15q22.2	*RORA*	123
15q22.33	*SMAD3*	108, 123
16p13.13	*CLEC16A*	123
17q12–21	*GRB7*, *IKZF3*, *ZPBP2*, *GSDMB*, *ORMDL3*, *GSDMA*	108, 109, 123, 137, 145, 156
22q12.3	*IL2RB*	108

This table is collated from the publicly available GWAS Catalog (19), listing all GWAS hits for asthma per se (excluding intermediate or compound phenotypes) with a p value $< 5 \times 10^{-8}$ at the time of writing.

Other loci achieving significant p values (i.e., below the genome-wide significance threshold of 5×10^{-8}) in multiple GWASs include a site on chromosome 2q12 in the vicinity of several interleukin receptor genes, namely *IL1RL1*, *IL1RL2*, and *IL18R1*. While these multigene loci are challenging to dissect, it is notable that *IL1RL1* encodes the receptor for IL33. The gene that encodes IL33 is separately implicated in the genetic etiology of asthma through a replicated locus on chromosome 9p24.1. IL33, a transcription factor and cytokine, is expressed in the airway epithelium, where it acts as a proinflammatory danger signal following its release from cells undergoing necrosis (resulting from infection or damage). Other widely observed sites of association include a region on 5q22.1 that contains the mitochondrial solute carrier gene *SLC25A46* and the hemopoietic cytokine gene *TSLP*, a complex region located within the major histocompatibility locus (6p21.32), the *C11orf30-LRRC32* site implicated elsewhere in an array of atopic traits (11q13.2), and the signal transducer and transcriptional modulator gene *SMAD3* (15q22.33).

A notable observation from GWASs of asthma is the profound lack of overlap between the results of early low-resolution linkage and positional cloning studies and those of subsequent high-resolution GWASs. Examination of the GWAS Catalog (19) shows that no marker positioned in or around the eight positionally cloned genes (**Table 1**) has yet achieved genome-wide significance for asthma, or even a more modest threshold of $p \leq 5 \times 10^{-6}$. Markers proximal to these genes do, however, achieve moderately low p values for a spectrum of alternative traits, including several of possible relevance to asthma. These traits include indices related to obesity (*DPP10*), inflammatory diseases of alternative epithelial surfaces (*HLA-G*), measures of lung function (*CYFIP2* and *NPSR1*), atopy (*HLA-G*), infection, and host–organism interactions (*DPP10* and *HLA-G*) (**Table 1**).

There are various explanations for this lack of overlap. Standard GWASs are not powered to capture linkage disequilibrium between typed variants and untyped variants of low minor allele frequency, while classic linkage studies are capable of detecting rare variants but require a larger effect size (high penetrance) to permit detection. Individual linkage signals may also reflect allelic and/or locus heterogeneity, with contrasting alleles or even genes underlying the signal in different pedigrees. These differences mean that the two approaches may target partially separable components of the genetic architecture and as such may account for an apparent lack of communality between the results of linkage studies and those of GWASs in asthma. However, the failure of GWASs to detect signals in regions implicated by linkage analysis may also suggest that the linkage represents a false positive, particularly when imputation of rarer untyped variants is included in the GWAS.

Asthma and Related Phenotypes

Epidemiological studies have shown that asthma commonly co-occurs at the level of the individual, or more broadly at the level of the immediate family unit, with a diverse spectrum of traits, from gastroesophageal reflux disease to obesity. These patterns of co-occurrence suggest a level of overlap in the underlying mechanisms of pathogenesis.

The atopic triad. Perhaps the most widely recognized pattern of co-occurrence is the one of asthma, atopic dermatitis (eczema), and allergic rhinitis (hay fever), which together are referred to as the atopic triad and characteristically present clinically in a temporal sequence known as the atopic march. Within this sequence, atopic dermatitis is typically the first component to manifest, with approximately 20–30% of individuals with mild disease and 70% of those with severe disease going on to develop asthma. Individuals who undergo this distinctive sequence of disease progression frequently exhibit a more severe and persistent phenotype, with increased risk of allergen sensitization.

All three of the atopic triad traits are strongly heritable (asthma, 35–95%; allergic rhinitis, 33–91%; and atopic dermatitis, 71–84%) (116) and show patterns of familial aggregation. The traits demonstrate marked (though incomplete) genetic correlations, indicating the presence of both shared and unique genetic influences (asthma–atopic dermatitis, 0.35–0.55; asthma–allergic rhinitis, 0.47–0.90; allergic rhinitis–atopic dermatitis, 0.62–0.73) (86, 140). The molecular mechanisms for this multi-morbidity are unclear. Comparison of susceptibility loci revealed by early linkage studies and subsequent single-trait GWASs provided little evidence of overlap. Indeed, a greater level of coincidence was reported between atopic dermatitis and the Th1-driven skin disease psoriasis, although this was antagonistic in nature (mapping to shared genes but opposing alleles) (148). Similar instances of inverse (antagonistic) association have been documented across a variety of disease pairings, from chronic obstructive pulmonary disease and pulmonary fibrosis (65) to inflammatory bowel disease (IBD) and type 1 diabetes (146), suggesting the possible presence of balancing selection at these genetic sites. Pleiotropic effects, whereby a single locus influences two or more traits, have been widely reported for atopic dermatitis. A recent GWAS observed pervasive sharing of loci (121). Almost 78% of atopic dermatitis–associated loci identified were implicated in alternative immune-mediated traits, from IBD to psoriasis and multiple sclerosis. While none of these genome-wide significant loci matched established sites of association to asthma per se, the authors reported that a third of established asthma loci achieved nominal significance levels in atopic dermatitis with an equivalent direction of effect. This suggests the possibility of small effect sizes in asthma that require substantial levels of power for detection at a genome-wide significance level.

More recent attempts to deconstruct the molecular mechanisms of the atopic triad multimorbidity have adopted two main approaches. The first is in silico, involving data mining and the construction of protein-level functional interaction networks. This strategy has shown that atopic triad diseases share a larger fraction of proteins and a greater level of interconnectedness than would be expected by chance (2). Specifically, five proteins (IL4, IL13, IL1RL1, IL18R1, and TSLP) and two cellular pathways (involving GATA3-related and IL4 signaling) were identified as common to all three atopic triad traits. *GATA3* is a recognized regulator of T cell development, while *TSLP* encodes thymic stromal lymphopoietin, a hemopoietic cytokine that promotes Th2 immune responses. Together, these data highlight a common theme of the type 2 response.

The second approach has involved conducting cross-trait GWASs using compound atopic triad phenotypes. Marenholz et al. (97) examined infantile atopic dermatitis followed by childhood asthma and identified seven contributory loci: 1q21.3 (*FLG*), 5q31.1 (*IL5/KIF3A*), 6p12.3 (*EFHC1*), 11q13.1 (*AP5B1/OVOL1*), 11q13.5 (*C11orf30/LRRC32*), 12q21.3 (*SLC6A15/TMTC2*), and 17q21 (*IKZF3*). Subsequently, Ferreira et al. (46) extended this approach in a substantial collection of more than 360,000 individuals, seeking genetic risk factors shared among all three atopic triad traits. The authors identified 136 independent risk variants underlying this shared risk, more than a third of which mapped to novel loci. Only a small minority of variants (4.4%) showed stronger effects in one atopic trait relative to the remaining two. These included *GSDMB*, located in the major chromosome 17q12–21 asthma locus (with risk variants relatively more common in asthma), and *FLG*, the most significant and replicable site of genetic association with atopic dermatitis to date (more common in atopic dermatitis).

Filaggrin, encoded by *FLG*, forms a key structural component of the terminally differentiated epidermis. The gene contains a spectrum of loss-of-function mutations that associate with asthma occurring in conjunction with atopic dermatitis but not asthma occurring independently of atopic dermatitis (118). These data alongside an absence of *FLG* expression in the airway epithelia (excepting the hair-bearing outer nasal cavity) suggest that, in the subset of cases bearing *FLG* mutations, asthma may be a secondary to a compromised, "leaky" skin barrier that allows

percutaneous transfer of allergens and pathogens. Consistent with this hypothesis, mice naturally deficient for filaggrin (the so-called flaky tail mutants) show increased levels of percutaneous allergen priming (43), and in humans, *FLG* mutations are additionally associated with increased rates of several Th2 phenotypes (such as food allergy) that manifest at sites anatomically remote to the epidermis (70).

Obesity. In addition to atopic traits, there is strong epidemiological evidence of an association between asthma and obesity, particularly in affluent countries. Obesity precedes the development of asthma, conferring a dose-dependent effect on asthma incidence (150). No consistent relationship, however, has been identified between excess weight and atopic status (125, 149), leading some to posit obese asthma as a separable disease phenotype (93). Proposed explanations for the epidemiological relationship between asthma and obesity include shared co-morbidities (such as gastroesophageal reflux disease) and/or shared pathological features (such as systemic inflammation, oxidative stress, or leptin resistance). The adipose-derived hormone leptin is a key metabolic signal and is typically observed at relatively increased levels in obesity. Leptin is associated with several immune functions and regulates airway diameter independently of inflammation (7), which is consistent with the relative inefficacy of anti-inflammatory agents in the treatment of obese asthma (122).

Asthma and obesity possess a modest genetic correlation of 0.29, accounting for approximately 8% of the total genetic component of obesity (59). The genetic underpinnings of this joint susceptibility are largely undefined, with a single exception: a common inversion on chromosome 16p11.2 (55) that affects the expression of a collection of genes participating in the regulation of energy balance and immunity. Analysis of GWAS signals relating to body mass index or asthma in asthmatics (a GWAS-informed candidate gene strategy) did not reveal any significant pattern of overlap (105). Likewise, attempts to map the shared genetic origins of asthma and obesity directly through GWASs have proven relatively unsuccessful. A GWAS of body mass index in 23,000 asthmatics yielded only limited evidence of a heterogeneous effect of *DENND1B* [an overall GWAS hit for asthma (129); see **Table 1**] in asthmatic children, an effect that could not be replicated outside of the discovery cohort (104). Equally, a GWAS designed to model the interaction between asthma and body mass index on a genome-wide scale identified no variants significant at a genome-wide threshold, although multiple variants in the classic asthma 17q21 locus were classified as suggestive (147).

Chronic obstructive pulmonary disease. Considering the adult age group, asthma can also overlap with chronic obstructive pulmonary disease (133). This disease is characterized by a progressive, refractory airflow limitation, typically associated with long-term tobacco smoke exposure. A genetic correlation of 0.38 is defined between chronic obstructive pulmonary disease and asthma (65). With the exception of the locus on chromosome 16p11.2, previously implicated in the joint susceptibility to asthma and obesity (55), GWASs have not yet revealed shared sites of association between asthma and chronic obstructive pulmonary disease (65).

Inflammatory bowel disease. Several parallels can be drawn between asthma and IBD. IBD encompasses two major clinical entities: Crohn's disease and ulcerative colitis. Both IBD and asthma represent chronic relapsing inflammatory phenotypes that affect mucosal epithelial surfaces, albeit remotely from one another (in the gastrointestinal and respiratory tracts, respectively). The diseases additionally share several risk factors. As with asthma, a lack of breastfeeding is associated with an increased risk of IBD, as is early exposure to antibiotics. Furthermore, there is now accumulating evidence of an elevated prevalence of asthma (and atopic dermatitis) in IBD, with a

diagnosis of asthma associated with significantly increased odds of early- and late-onset ulcerative colitis as well as Crohn's disease (76). Familial clustering of IBD is consistent with a genetic component, with pooled twin studies indicating a heritability of 0.75 for Crohn's disease and 0.67 for ulcerative colitis (56). While the genetic correlation between asthma and IBD is not, to the best of our knowledge, currently defined, evidence supporting the presence of genetic overlap dates back to early linkage studies (26).

More recent attempts to map the genetic determinants of IBD (IBD overall or its two major clinical entities separately) through GWASs confirmed genetic intersection between these traits, identifying at least 11 sites of association ($p < 5 \times 10^{-8}$) coincident with those described by asthma GWASs: chromosomes 1q25.1 (*TNFSF18* and *TNFSF4*) (13, 49, 72), 1q31.3 (*DENND1B* and *CRB1*) (32, 49, 72, 87), 2q12 (*IL18R1*, *IL1RL1*, and *IL1RL2*) (32, 49, 72, 87), 3q28 (*LPP*) (32), 5q31 (*NDFIP1*) (32, 49, 72, 87), 6p21.32 (*PBX2*, *NOTCH4*, *C6orf10*, *BTNL2*, *HLA-DRA*, *HLA-DRB5*, *HLA-DQA1*, and *HLA-DQA2*) (5, 8, 32, 47–49, 72–74, 77, 87, 102, 128, 138, 155, 158, 159), 6p21.33 (*HLA-C* and *MICA*) (32, 72, 73), 6q15 (*BACH2*) (32, 49, 72, 87), 11q13.5 (*C11orf30*) (5, 13, 32, 49, 72, 87), 15q22.33 (*SMAD3*) (32, 49, 72, 87), and 17q12–21 (*GRB7*, *IKZF3*, *ZPBP2*, *GSDMB*, *ORMDL3*, and *GSDMA*) (5, 13, 32, 49, 72, 87, 102) (**Table 2**). Among these sites, the 17q12–21 locus has received considerable research attention because it is the most significantly associated locus for asthma; shows replicable association with ulcerative colitis, Crohn's disease, and IBD overall; and coincides with the most significant Crohn's disease–associated eQTL (13). Other loci of interest include *SMAD3*, which encodes SMAD family member 3, a signal and transcriptional modulator that is responsive to transforming growth factor β (TGF-β) and is therefore key to the TGF-β-mediated epithelial-to-mesenchymal transition and fibrosis. Similarly, *BACH2* (BTB domain and CNC homolog 2) encodes a transcription factor essential for T and B lymphocyte differentiation. *C11orf30* encodes the nuclear protein EMSY, which has postulated roles in epithelial immunity, growth, and/or differentiation (41). *C11orf30* has also been implicated in a range of atopy-related traits, from polysensitization to atopic dermatitis, eosinophilic esophagitis, and total serum IgE. Together, these data indicate substantial levels of genetic communality between IBD and asthma and direct emphasis toward the mucosal immune barrier in these diseases.

Asthma and Infection

A role of early severe viral respiratory infections in the development and exacerbation of asthma in children is widely recognized, particularly with regard to the respiratory pathogens rhinovirus and respiratory syncytial virus (52). Both of these viruses are early predictors of recurrent wheezing, with early rhinovirus-related wheeze predictive of subsequent asthma (88). The mechanism for this phenomenon, however, is poorly defined. Evidence of host genetic factors in respiratory tract infectious diseases is controversial, marred by issues of bias and confounding (120). A recent meta-analysis of 386 studies targeting infectious diseases of the respiratory tract nonetheless highlighted a role for the *IL4-TLR2-CCL2* axis, with *IL4* sequence variants achieving significance in a pooled model, indicating shared host effects common to multiple respiratory infections (120). Notably, sequence variants proximal to *IL4* have previously been implicated in the etiology of asthma through candidate gene association studies (see above). Mice deficient for *IL4* show increased susceptibility to some respiratory pathogens as well as increased mortality (110), consistent with the gene's role in host–pathogen dynamics. A direction of focus onto the mucosal barrier arising from GWASs adds weight to the rationale for investigating viral and other microbial infections in asthma and underscores the importance of ensuring that such data are captured efficiently at the time of study population collection.

EPIGENOME-WIDE ASSOCIATION STUDIES

The term epigenetics describes changes in gene activity and/or function that do not involve alteration of the DNA sequence. DNA methylation was the first epigenetic change to be widely studied, following the observation that CpG methylation is associated with gene silencing and the patterning of gene expression that determines cellular types and functions (33). CpG sites represent positions in the DNA sequence in which a cytosine nucleotide and a guanine nucleotide are separated by a single phosphate group when read in the 5′-to-3′ direction (5′-C-p-G-3′). CpG islands encompass broader regions of DNA that contain a relative enrichment of CpG sites. Epigenetic investigations also include modifications of the histones and other regulatory elements that bind to DNA [exemplified in the Encyclopedia of DNA Elements (ENCODE) project].

While the original coinage of the term epigenetics implied epigenetic inheritance (e.g., at loci showing genomic imprinting), the vast majority of epigenetic modifications are not heritable. In general, epigenetic alterations can be considered responses to environmental influences, providing exposure-dependent plasticity in gene activity or function. Although epigenetically modified genes and pathways may be central to disease pathobiology, they are likely to represent changes in gene regulation in response to environmental or other factors and are not causal of disease susceptibility in the same way as true genetic variants.

Further factors that should be considered in interpreting epigenome-wide association studies (EWASs) are the distinctive epigenetic patterns of particular cell types and the cellular heterogeneity present in peripheral blood and different tissues (84). In contrast to genetic studies, where polymorphisms are a constant feature of DNA derived from any tissue of the human body, epigenetic modifications contain strong cell-specific signatures. Consequently, for example, peripheral-blood leukocytes may not contain core epigenetic events that are present in asthmatic airways or eczematous skin.

While it has been suggested that generalized abnormalities of methylation may be present in asthma (12), the hypothesis has subsequently not gained support. Well-powered EWASs that have controlled for cellular heterogeneity have, however, generated some consistent and interesting results that indicate the importance of particular pathways and cell types in the etiology of atopic asthma.

Epigenetic Features of Asthma: Outside of the Lung

In 2015, Liang et al. (85) surveyed epigenetic associations between serum IgE concentrations and methylation at loci concentrated in CpG islands in 95 nuclear pedigrees, using a first-generation Illumina methylation array to test DNA from peripheral-blood leukocytes. They validated positive results in additional families and a general population sample. Replicated associations (false discovery rate $<10^{-4}$) were found between IgE and low methylation at 36 loci. Many genes annotated to these loci encode known eosinophil products (in particular *IL5RA*, encoding the eotaxin receptor), whereas other associations implicated phospholipid inflammatory mediators (such as the one encoded by *LPCAT2*), specific transcription factors, and mitochondrial proteins (such as the one encoded by *L2HGDH*).

Modeling of the association with differential white cell counts showed that 10% of the variation in IgE level was attributable to eosinophil counts and that the top three loci (indicating the level of eosinophil activation) accounted for a further 13% of IgE variation. The authors confirmed eosinophil activation by showing that methylation in isolated eosinophils differed significantly in subjects with and without asthma and high IgE levels.

A subsequent study of approximately 1,000 children from the Avon Longitudinal Study of Parents and Children assessed associations of asthma and wheeze with DNA methylation at 450,000 sites (using an Illumina methylation array), extending the tests for differentially methylated regions beyond CpG islands. Samples were taken at 7.5 and 16.5 years of age (6). The authors identified 302 CpGs associated with current asthma status (false discovery rate–adjusted p value $<$ 0.05) and 445 associated with current wheeze status at 7.5 years, with substantial overlap between the two. Genes annotated to the 302 associated CpGs were related to IL4 production and eosinophil migration. As with the adult EWAS (85), the associations were attenuated when adjusted for eosinophil and neutrophil cell count estimates. At 16.5 years, two sites, mapping to the *AP2A2* and *IL5RA* genes, remained associated with current asthma after adjustment for cell counts.

Epigenome-wide DNA methylation was most recently investigated in the whole-blood DNA of asthma cases and controls at ages 4–8 years from four European birth cohorts within the Mechanisms of the Development of Allergy project (153). Cell type specificity was addressed in eosinophils and nasal epithelial cells. Consistently lower methylation levels were observed at 14 loci that showed genome-wide significance in meta-analyses; all of the loci were associated across childhood from ages 4 to 16 years but not at birth. All 14 CpGs were significantly associated with asthma in a replication study using whole-blood DNA and were strongly associated with asthma in purified eosinophils. Whole-blood transcriptional signatures associated with these CpGs indicated increased activation of eosinophils, effector/memory CD8-T, and natural killer cells and reduced naive T cells. Of the 14 CpGs, 5 were associated with asthma in respiratory epithelial cells, indicating cross-tissue epigenetic effects. These CpGs and their associated transcriptional profiles suggest activation of eosinophils and cytotoxic T cells in childhood asthma, consistent with early-life microbial exposures.

A smaller study of methylation in cord blood (36) found that methylation in *SMAD3* was selectively increased in asthmatic children of asthmatic mothers and was associated with childhood asthma risk. As highlighted above, GWASs of asthma have found *SMAD3* to be important, and further analyses may be necessary to separate the epigenetic changes from the effects of heritable polymorphism.

EWAS association between genome-wide DNA methylation in whole-blood cells and total IgE levels has been examined in two panels of Hispanic children (22). The results confirmed many associations with total IgE levels previously reported in Caucasians. As with other investigations, adjustment for whole-blood cell types resulted in markedly fewer significant sites. Top novel findings from an adjusted meta-analysis were in the genes *ZFPM1* ($p = 1.5 \times 10^{-12}$), *ACOT7* ($p = 2.5 \times 10^{-11}$), and *MND1* ($p = 1.4 \times 10^{-9}$).

Overall, the above EWASs have identified consistent sets of markers that show activated eosinophils to be of particular importance in childhood asthma and adult asthma when accompanied by a high serum IgE level. Eosinophils develop in the bone marrow and are activated and recruited into tissues in response to stimuli that include IL5 and eotaxin (126). IL5 and its specific receptor subunit, IL5RA, are therapeutic targets for asthma, and these epigenetic findings validate drugs that include benralizumab (which binds to IL5RA) and the humanized IL5-specific antibodies mepolizumab and reslizumab. These biologics are very expensive (on the order of US$30,000 per patient each year), and as such, assays for measuring the level of activation of IL5RA may become of value in predicting which patients will respond to treatment. Alternatively, the *LPCAT2* gene, implicated by Liang et al. (85), may define a way to treat asthma with small-molecule antagonists that will prevent the stimulus-dependent formation of the potent proinflammatory lipid mediator platelet-activating factor (PAF) (127).

Epigenetic Features of Asthma: Within the Lung

A study of the epigenome in primary airway epithelial cells from 74 asthmatic and 41 non-asthmatic adults (111) revealed a regulatory locus on chromosome 17q12–21 (the same locus identified by asthma GWASs) associated with asthma risk and epigenetic signatures of specific asthma endotypes. *ORMDL3* expression was related to the differentially methylated region at this locus, while the expression of *GSDMB* was not. A differentially methylated region near *CCL26* (encoding eotaxin 3) also had a significantly associated eQTL. This important study reminds us that asthma is primarily a disease of the airways, whereas effects in peripheral-blood leukocytes reflect changes in the circulating immune system. This may explain why the peripheral-blood leukocyte studies outlined above primarily reported strong associations with the total serum IgE, with relatively weak findings for asthma itself. Despite the technical challenges of obtaining samples from within the lung, further genomic and methylation studies of the airway epithelium appear necessary to enable the field to move forward.

TRANSCRIPTOMICS

The development of array-based and, subsequently, RNA sequencing technologies has fostered high-throughput transcriptomic analyses of asthma across a host of cell populations, time frames, and exposure conditions.

Transcriptomics as a Tool for Defining the Impact of Disease on a Tissue or Cell System

In one of the first large-scale, genome-wide gene expression studies of asthma, Dixon et al. (38) characterized the transcriptomes of peripheral-blood leukocyte–derived lymphoblastoid cell lines of children with and without asthma and examined the relationship between transcript abundance and genotype. Clear patterns of heritability were observed, with more than 15,000 transcripts demonstrating a narrow-sense (h_2) heritability greater than 0.3, including both local and distal effects and clear patterns of enrichment for specific biological processes. Nonetheless, only 10 transcripts showed significant disease-related differences in abundance, and none of these retained significance following adjustment for multiple comparisons. This result is perhaps unsurprising given the context in which disease-related differences in gene expression were sought—i.e., unchallenged, immortalized cultured cell lines. Nevertheless, the authors were able to confirm that asthma-associated markers in the 17q23 region account for 29.5% of variance in *ORMDL3* expression, supporting *ORMDL3* as a major candidate gene in this region.

Transcriptional signatures of asthma have since been sought in a variety of minimally invasive disease-relevant tissues, ranging from sputum (157) to whole blood (16, 27) and bronchial brushings (91). Peripheral-blood data sets suggest the presence of replicable transcriptomic signatures relating to the extent of asthma control, with the strongest and most highly reproducible enriched gene sets expressed by specific immune cell lineages, including 11 eosinophil-specific gene sets (suggesting parallels with EWAS data) (27). Whole-blood results also indicate variation in gene expression by disease severity, with a substantially greater magnitude of differential expression documented between healthy subjects and severe asthmatics than between healthy subjects and those with mild or moderate disease. However, similar gene sets have been reported as affected in both comparisons, suggesting a disease-severity-related transcriptomic continuum (16). That said, in their 2016 analysis of the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohorts, Bigler et al. (16) showed that the number of differentially expressed genes

in whole blood was dramatically cut (by as much as 90%) when blood cell counts were included as covariates, suggesting that the majority of differential expression may be accounted for by disease-related changes in peripheral-blood composition.

Shifting the compartment of study from peripheral blood to the epithelial barrier, in 2017 Loffredo et al. (91) performed a comparative analysis of publicly available transcriptomic data sets of asthma from bronchial epithelial cells. The authors identified a consensus signature of 159 core genes differentially expressed by disease status with a consistency in directionality across the majority of studies (five of the eight studies analyzed). Functional pathway analysis of these genes revealed a close-knit interaction network, with key features highlighting themes of epithelial–mesenchymal imbalance, remodeling, and dedifferentiation. Traditional markers of epithelial-to-mesenchymal transition were notably absent; instead, *EFNB2*, *FGFR1*, *FGFR2*, *INSR*, *IRS2*, *NOTCH2* (participating in ephrin, insulin, and Notch signaling), *NTRK2*, and *TLE1* were identified as central components of the interaction network. Key genes were differentially expressed across the full spectrum of disease severity and showed progression along the disease-severity gradient. Moreover, similar gene expression patterns could be approximated in organotypic air–liquid interface culture conditions via insulin depletion. These gene expression data support a hypothesis of barrier dysfunction in asthma and suggest the possibility that this dysfunction may be secondary to systemic factors (such as insulin insufficiency or resistance).

Transcriptomics as a Tool for Pathway or Candidate Gene Exploration

We have highlighted above that transcriptomics offers an unbiased method of characterizing pathways and their composite transcripts perturbed in the context of asthma, as well as cross-tissue and inter-subgroup comparisons. In addition, however, transcriptomics offers a valuable opportunity to catalog the impact of experimentally manipulated endogenous or exogenous factors on a cellular system, or to simply track gene expression patterns through key developmental stages or processes. Widely applied experimental manipulations include controlled knockdown of a single candidate gene, exposure to a known risk factor (e.g., microbial stimuli or organic or nonorganic airborne particulates), or a combination of the two.

By way of example, the process of class-switch recombination from IgA/IgG/IgM to IgE is of central importance to atopic diseases such as asthma, since it is required for B cells to express IgE. In 2016, Zhang et al. (161) monitored global gene expression and exon retention during the activation of immunoglobulin class switching in human B cells. The authors identified a complex yet organized transcriptional cascade accompanying the process of class-switch recombination, including genes known to participate in the moderation of circadian rhythms (*BHLHE40* and *NFIL3*). The involvement of clock genes is notable since circadian oscillations represent a prominent feature of asthma symptoms (39), and experimental deletion of an alternative clock gene (*BMAL1*) recently revealed links between the circadian clock and both viral airway pathology and asthma phenotypes (40).

The role of viral respiratory infection in asthma is a major area of emerging interest (see the section titled Asthma and Infection). To this end, Etemadi et al. (42) recently profiled the transcriptional response to rhinovirus infection in human alveolar epithelial cells. These data, derived from a controlled in vitro system, revealed a substantial impact of rhinovirus infection on global gene transcription, with distinct functional categories showing enrichment at the various stages of the infection time course, including an early inflammatory chemokine response. The most strikingly upregulated gene across all time points was the transcriptional regulator gene *EGR1* (early growth response 1), implicated elsewhere in the transcriptional response to smoke exposure in the nasal mucosa (99).

Considering the process of lung development, Melén et al. (106) queried publicly available gene expression data sets that had assayed gene expression in the developing human or murine lung, and sought overlap with known asthma candidate genes. Candidate genes were not significantly overrepresented among developmentally regulated genes, but a small minority of candidates did demonstrate differential expression and consistent temporal trends in both mice and humans. These included *NOD1*, *EDN1*, and *CCL5*, as well as the positionally cloned *HLA-G* and *RORA* genes, both of which have more recently been identified to be of importance by asthma GWASs. These data cumulatively add context to existing associations and suggest possible roles in lung development or morphogenesis.

THE LUNG MICROBIOME

It has long been hypothesized that microbiotas play a key role in the etiology of asthma and, more broadly, atopic disease. The prevalence of asthma has increased dramatically over recent decades in parallel with a decline in the rates of infectious disease. These changes accompany improvements in sanitation, cleanliness, and vaccination. Small family sizes, birth by caesarian section, and urban living all represent risk factors for asthma, while early farm exposures and breastfeeding confer protective effects. Such observations have been assimilated into the hygiene hypothesis, first set out in 1989 (136), positing that reduced early microbial exposure and its impacts on immunity underlie the post–Industrial Revolution atopy and asthma epidemic. Responsible for a transformation in our understanding of microbial factors in asthma has been a revolution of a different kind. Only approximately 5% of bacteria can be cultured in the laboratory through standard techniques—the so-called great plate count anomaly (135). By contrast, next-generation sequencing approaches, which make use of the balance between sequence conservation and variation in the bacterial 16S rRNA gene, enable the isolation and accurate identification of most microorganisms. The technique has been successfully applied to the upper and lower airways as well as the gut and has provided novel insights into the role(s) played by bacteria in asthma.

Historically, the lung was considered a sterile landscape. Application of culture-independent techniques has, however, shown that neither the upper nor the lower airways can be considered sterile in either health or disease (asthma, chronic obstructive pulmonary disease, or idiopathic pulmonary fibrosis) (reviewed in 95). Moreover, accumulating evidence suggests that colonization of some anatomical sites may even precede birth, being initiated in utero (1, 23). In health, microbiotas detected in the lung demonstrate considerable overlap with those seen in the upper airways (14, 98), arguably consistent with microaspiration as a source of lung microbiotas. In disease, the overlap between the upper airways and lung is less clear (37, 61).

Culture-independent microbiome profiling specifically in asthma has revealed significant differences between cases and controls in the lower airways, in particular with regard to members of the gram-negative phylum Proteobacteria (54, 61). Interestingly, *Haemophilus parainfluenzae*, also a member of the Proteobacteria phylum, appears to promote blunt corticosteroid responses through activation of the TAK1/MAPK pathways, suggesting a possible microbial mechanism for corticosteroid resistance in asthma (54). While a role for Proteobacteria in asthma is contentious, data from murine models also highlight weak inflammatory properties of airway commensals (accounting for their tolerance), while asthma-associated Proteobacteria trigger lung inflammation and associated pathology (79).

CONCLUSIONS: A GENOMIC VIEW OF ASTHMA

The field of asthma genetics has changed dramatically over the last decade. Technological advancements have brought with them the tools with which to interrogate the human genome,

epigenome, and transcriptome, as well as the microbial flora of humans, with unprecedented accuracy and volume. This toolbox has facilitated the stepwise accrual of information regarding the pathogenic mechanisms of asthma, free from hypothesis or bias, and enabled direct comparison between diseases. The challenge now is twofold: first, generating a meaningful synthesis of these data, which are both substantial and diverse, and second, explaining the considerable proportion of asthma heritability that remains unaccounted for despite the volume of existing data—challenges that are closely interwoven.

At the time of writing, GWASs alone have yielded at least 38 genomic loci that show association with asthma with *p* values that meet or exceed the widely applied genome-wide threshold for significance of 5×10^{-8}. These loci show little to no correspondence with the eight previously positionally cloned asthma susceptibility genes, and likewise, historical candidate genes do not feature prominently in asthma GWAS results. The explanation for this lack of intersection may in part be statistical, reflecting the presence of false positives among reported susceptibility genes. This is not, however, the only possible explanation; also likely to be influential are a disparity in the types of effects that are amenable to capture by the techniques of linkage and association (including the potential role of rare variants) and the overarching role of unmeasured variation. The latter encompasses the phenotype itself, the underlying genetic architecture, and salient environmental exposures.

Epidemiological data have clearly demonstrated the relevance of a broad spectrum of environmental factors in the etiology of asthma, from tobacco smoke exposure to early respiratory infection and birth by caesarian section. More recent analyses of the lung microbiome in asthma have built on these observations, indicating a dysbiosis in disease and controversially highlighting a significant role for Proteobacteria. The participation of environmental factors in the etiology of asthma renders gene × environment interaction a plausible explanation for inconsistent replication between cohorts. Indeed, analyses of the major asthma locus on chromosome 17q12–21 have revealed evidence of interplay with several exogenous factors, including early respiratory infection (130) and early passive environmental tobacco smoke (17), the latter of which has been independently replicated (141). Since narrow-sense heritability estimates may be inflated by the presence of nonadditive effects (96), gene × environment interactions may plausibly contribute to the issue of apparent missing heritability. Today, gene × environment interactions are being modeled on a genome-wide scale through GWASs (143), but the success of such approaches will be tied to the selection and precise measurement of pertinent environmental exposures, the collection of information regarding their temporal sequence, and the generation of sufficient statistical power. Clarification of the relevant environmental influences in asthma may therefore be warranted, enabling more straightforward identification and replication of environmentally malleable genetic effects.

A second observation from the genetic studies of asthma has been the genetic correlation between asthma and a range of other phenotypes, and thence the accompanying overlap in susceptibility genes or variants. Analyses of this overlap have already afforded some insights into shared mechanisms, e.g., pointing to the mucosal immune barrier in IBD and the type 2 response in atopic triad diseases. Indeed, in some cases, such as the epidermal barrier gene *FLG*, association with asthma appears to occur only within the context of a second trait (in the case of *FLG* atopic dermatitis). Such observations underscore the importance of patient stratification and clear phenotype definition in study design and lend weight to the notion that asthma is both genetically and clinically heterogeneous. Unfortunately, in the majority of cases, the effect size conferred by any given risk variant is relatively low, limiting their individual utility for distinguishing patients in a clinical setting. Nevertheless, these variants and their patterns of pleiotropy provide valuable information on the mechanisms of disease causation and co-morbidity. Unlike the cancer field

(notably breast cancer), the field of asthma remains at some distance from personalized medicine, but it appears likely that at least a subset of genes that affect asthma susceptibility also influence risk for other disease traits. Furthermore, transcriptomic data suggest that blood-based transcriptional signatures exhibit relationships with features of asthma itself, such as disease severity or control.

Transcriptomic screening provides a systematic technique for assessing the impact of a single gene (through experimental up- or downregulation) on a cellular system, and this will be key to understanding the roles of asthma susceptibility genes defined to date. Such techniques are already widely applied for cataloging the transcriptional underpinnings of disease-relevant processes, be it class-switch recombination in B cells or response to infection in alveolar epithelial cells. Moving toward a more complete understanding of the genetic basis of asthma will require characterizing the role(s) of established susceptibility genes through these and other similar techniques, as well as focusing on patient stratification and characterization of environmental influences.

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