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The Genetics of Asthma and Allergic Disease: A 21st Century Perspective

Carole Ober[1] and **Tsung-Chieh Yao**[2]

[1]Department of Human Genetics, The University of Chicago, Chicago, IL, USA

[2]Division of Allergy, Asthma, and Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan

Summary

Asthma and allergy are common conditions with complex etiologies involving both genetic and environmental contributions. Recent genome-wide association studies (GWAS) and meta-analyses of GWAS have begun to shed light on both common and distinct pathways that contribute to asthma and allergic diseases. Associations with variation in genes encoding the epithelial cell-derived cytokines, interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP), and the *IL1RL1* gene encoding the IL-33 receptor, ST2, highlight the central roles for innate immune response pathways that promote the activation and differentiation of T-helper 2 (Th2) cells in the pathogenesis of both asthma and allergic diseases. In contrast, variation at the 17q21 asthma locus, encoding the *ORMDL3* and *GSDML* genes, is specifically associated with risk for childhood onset asthma. These and other genetic findings are providing a list of well-validated asthma and allergy susceptibility genes that are expanding our understanding of the common and unique biological pathways that are dysregulated in these related conditions. Ongoing studies will continue to broaden our understanding of asthma and allergy and unravel the mechanisms for the development of these complex traits.

Keywords

association studies; linkage studies; GWAS; asthma; allergic disease; atopy

Introduction

Asthma and allergy are common conditions with complex and heterogeneous etiologies. Asthma and allergic disease often co-occur in the same individual or in different individuals within the same families. However, whether this co-occurrence reflects distinct conditions with shared pathogenic pathways or different clinical manifestations of the same disease is currently unknown.

Both asthma and allergic diseases (defined below) have significant genetic contributions, with heritability estimates varying between 35% and 95% for asthma (1-15), 33% and 91% for allergic rhinitis (hayfever) (2, 11-16), 71% and 84% for atopic dermatitis (eczema) (12-14), 35% and 84% for total serum immunoglobulin E (IgE) levels (9, 17-36), 34% and 68% for specific serum IgE levels (33-38), 30% and 66% for bronchial hyperresponsiveness (BHR) (32, 35, 36), and 24% to 41% for blood eosinophil counts (26, 35-37, 39). Overall,

Address for correspondence: Carole Ober Department of Human Genetics 920 E. 58th Street, CLSC 425 The University of Chicago Chicago, IL 60637 Tel: +1 773 834 0735 Fax: +1 773 834 0505 c-ober@genetics.uchicago.edu.

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therefore, significant proportions of the inter-individual risks for these conditions are due to genetic differences. Nonetheless, identifying specific genes and variation within those genes that account for this risk has been one of the major challenges in asthma/allergy research over the past 40 years. Characterizing the genetic architecture of these conditions is the first step in beginning to understand whether they share a common etiology (i.e. different manifestations of the same disease) or overlapping pathogenic pathways (i.e. different diseases due to perturbations of a shared pathway). Recent genetic studies are beginning to shed light on this important question.

In this review, we summarize the genetic studies of asthma and allergic diseases that have been conducted over the past 40 years, with emphasis on studies completed in the past 5 years and, in particular, on results of genome-wide association studies (GWAS). Ultimately, we will discuss these results in light of the relationship between asthma and allergic diseases.

Asthma and allergic diseases

Allergy refers to a detrimental immune-mediated inflammatory response to normally harmless environmental substances known as allergens, resulting in one or more allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, and food allergy. In contrast, atopy is defined by evidence of allergic sensitization to known allergens, reflected in either a positive skin prick test (SPT) or the presence of specific IgE to one or more known allergens in the serum. Elevated total serum IgE is sometimes also used as a proxy for atopy. The relationship between allergic diseases and atopy is complicated by two facts: not everyone with atopy develops clinical manifestations of allergy and not everyone with clinical symptoms of allergic disease is atopic when tested for specific IgE to a wide range of environmental allergens (40). In this section, we focus on the epidemiology and burden of asthma and allergy, as well as the heterogeneous nature of the asthma phenotypes, and highlight the link between asthma and allergic diseases.

Epidemiology and burden of asthma and allergy

The increase in the prevalence of asthma and allergic diseases in most countries around the world in recent decades poses a substantial global health burden to people of all ages and all ethnic backgrounds. The global prevalence of asthma ranges from 1% to 18% of the population in different countries (41-45). It is estimated that asthma affects as many as 300 million people worldwide; this is expected to increase to 400 million by 2025 (41, 42). Asthma is estimated to account for 1 in every 250 deaths worldwide, resulting in 250,000 deaths each year worldwide (41, 42). Allergic rhinitis, clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation, affects 10% to 20% of the population, with an estimated over 500 million affected people worldwide (46, 47). Atopic dermatitis, a chronic inflammatory pruritic skin disease, affects 10% to 20% of children and 1% to 3% of adults worldwide (48-50). Food allergy, defined as an adverse immune response to food proteins, affects up to 6% of young children and 3% to 4% of adults (51). The prevalence of allergic sensitization (based on positive SPT to allergens or the presence of allergen-specific serum IgE) ranges from 16% to 57% in the populations of the United States, Europe, Australia, New Zealand, and Taiwan (52-56). Allergic diseases cause widespread morbidity, leading to impaired work productivity and school performance, reduced quality of life, and substantial medical and non-medical costs.

Asthma: a complex, multifactorial disease

Asthma is a complex syndrome characterized by the presence of chronic inflammation in the lower airways, resulting in variable airflow obstruction and BHR and causing recurrent

episodes of coughing, wheezing, breathlessness, and chest tightness (41, 57). Because the pathogenesis of asthma is unknown and there are no tests or biomarkers that definitively diagnose asthma or distinguish it from other diseases, diagnosis is based on clinical features, demonstration of reversible expiratory airflow obstruction (or BHR when lung function is normal), and exclusion of alternative diagnoses that mimic asthma (41, 57). It is important to note that although tests for BHR are sensitive for a diagnosis of asthma, they have limited specificity (58). Therefore, a negative test may help exclude a diagnosis of current asthma in a subject who is not taking asthma medications. However, a positive test does not indicate that a subject has asthma (59), and BHR may be caused by conditions other than asthma, such as allergic rhinitis (60), chronic obstructive pulmonary disease (COPD) (61), and cystic fibrosis (62). Allergic sensitization commonly occurs in 80% of asthmatic children and approximately 60% of asthmatic adults (63). Tests for allergic sensitization may identify allergic triggers that cause asthma symptoms in individual patients, but individuals with allergic sensitization may develop other allergic diseases, and some sensitized individuals may never experience allergic symptoms (64, 65). Thus, skin prick tests or measurements of specific IgE are also not specific for a diagnosis of asthma or even for allergic diseases.

Clinical heterogeneity and intermediate phenotypes

Asthma is not a single disease but rather an umbrella for multiple diseases with similar clinical features, and likely with different genetic and environmental contributors. On the one hand, more precise phenotypic definitions would allow identification of more homogeneous subgroups of patients with asthma and facilitate genetic studies. On other hand, the discovery of asthma and allergy susceptibility loci could provide insights into phenotypic subgroups and ultimately inform the selection of targeted/effective treatment. Because of this clinical heterogeneity and challenge in defining asthma subgroups, intermediate phenotypes that can be measured more objectively are often the focus of genetic studies (66-73). These phenotypes include BHR, lung function, serum IgE, allergen skin test response, and blood eosinophil count, as described in Table 1. Genetic studies of intermediate phenotypes may ultimately facilitate the discovery of susceptibility genes for asthma or allergic diseases (66-68), or they may only identify genes that influence normal variation in the trait itself.

Link between asthma and allergic diseases

The clinical relationship between asthma, allergic rhinitis, and atopic dermatitis, the so-called ‘allergic triad’, is well known (74). These diseases often have their roots during childhood. Several longitudinal studies provide evidence for a characteristic sequential development of atopic manifestations during childhood: atopic dermatitis and food allergy typically develop in infancy followed by asthma and/or allergic rhinitis in childhood. This is referred to as the ‘atopic march’ (75-80). About 30% of children with atopic dermatitis develop asthma, and nearly 66% develop allergic sensitization and symptoms of allergic rhinitis (81). The vast majority (~80%) of patients with asthma have allergic rhinitis, whereas 19% to 38% of patients with allergic rhinitis have coexisting asthma (82-84). Of particular note is that asthma and allergic rhinitis are linked by common epidemiologic, clinical, and pathophysiologic mechanisms, as well as common comorbidities and therapeutic approaches, leading to the concept of ‘one airway one disease’ (47, 85-88), although also differences have also been noted (89). Yet, an open question remains as to whether asthma and allergic diseases are part of the same disease continuum, the ‘atopic syndrome’, occurring in different organs in the body, or they are distinct disease entities that have their own specific causes.

Environment modifiers of asthma and allergy

Asthma and allergy are caused by the complex interplay between genetic factors and environmental exposures that occur at critical times in development. Epidemiologic studies have highlighted many associations between environmental exposures and subsequent risk for asthma and allergy. Modifiers of risk that have been reported in the literature include genetics (discussed below), race/ethnicity (90), sex (91), passive (92-96) and active (97-99) tobacco smoke exposure, farm animals and related products (100-104), domestic cats and dogs (105-108), family size and birth order (109-112), daycare attendance in early childhood (113-115), respiratory viral infections (116-119), microbial exposures (120), vaccination (121-124), antibiotics and antipyretics (125-129), mode of delivery (130-133), breastfeeding (134-137), intake of diet and nutrition (138-143), air pollution (144-146), obesity (147-149), allergens (150-152), and occupational exposures (153-155). Further research is needed to clarify the importance of each and to elucidate the mechanisms through which each of these factors modifies risk for asthma and allergy.

Approaches for discovering asthma and allergy genes

The approaches used for asthma and allergy gene discovery have evolved over time as the various genotyping technologies have become both more high throughput and less costly. As we begin to adopt 21st century technologies, such as Next Generation sequencing (156) of whole genomes, gene discovery will no longer be limited by genotyping technologies but rather by the enormous computational and bioinformatic demands, and the interpretation and synthesis of the vast amounts of data generated by these approaches. In this section, we take a historical perspective and review the approaches that have been used to discover or better characterize asthma and allergy susceptibility loci. A summary of these approaches is shown in Table 2. We finish this section with a discussion of the implications of using each approach for gene discovery.

Candidate gene association studies

Candidate gene association studies are conceptually straightforward. The most common approach is a case-control study in which one searches for an enrichment of a marker (e.g., single nucleotide polymorphisms (SNPs) or insertion deletion (indel) polymorphisms) allele or haplotype (combination of alleles) in cases (individuals with a specific disease) compared to controls (either individuals without the disease, referred to as ‘super controls’, or subjects from the general population for whom disease status is unknown, referred to as ‘population controls’). Alternative approaches are cohort and cross-sectional study designs in which individuals are not selected on the basis of disease status. In these studies, one searches for an enrichment of the disease in individuals with a certain genotype at the marker locus or haplotype. The effect sizes of associated alleles, genotypes, or haplotypes are typically reported as either odds ratios (ORs) for case-control studies or relative risks (RRs) for cohort and cross-sectional studies.

As its name implies, genes are selected for these studies based on their known function (functional candidates), or their chromosomal position in a linkage peak (see ‘Genome-wide linkage studies’ below) or near a previous association signal (positional candidate). The specific variants used in candidate gene studies can be selected based on function (for example, an amino acid substitution that is known to influence protein function or a promoter SNP that is known to influence transcription), previous associations with the same or related disease, or to comprehensively survey variation in and around the gene of interest (which may also include the first two categories of variants). The latter strategy requires knowledge about the haplotype structure of the gene and the ability to select SNPs that ‘tag’ all common haplotypes. Such ‘tag SNPs’ would not be in strong linkage disequilibrium

(LD) with each other but would be selected to be in LD with other SNPs that are not genotyped in the sample (see references (157-159) for further description of this strategy). Thus, a relatively small number of SNPs (10 to several hundred depending on the size of the gene, the haplotype structure, and the stringency used for determining LD) are selected for each gene. Because genes are selected based on prior hypotheses (related to function or position or both), associations discovered by this method are easy to interpret. The latter is one of the advantages of candidate gene association studies.

The vast majority of genetic studies of asthma and allergic diseases have been candidate gene association studies in which genes were selected based on their known function and likely involvement in pathogenesis, as previously reviewed (160-162). As a result, these studies are heavily biased towards studies of immune-related genes. In fact, the most significant limitation of this approach is that it is confined to what we know (or what we think we know) about disease pathogenesis and gene functions. The candidate gene approach cannot, by itself, discovery novel pathways or genes.

Genome-wide approaches—In contrast to candidate gene association studies, the other gene discovery approaches that we will discuss are genome-wide approaches, which consider all regions of the genome without any prior hypotheses about the location of the most significant genetic contributors to risk. As a result, genome-wide approaches are referred to as ‘hypothesis-free’ or ‘hypothesis-generating’. The greatest advantage of genome-wide approaches is that they can discover novel genes and pathways involved in disease pathogenesis. The greatest limitation of these approaches is the statistical burden that results from the large number of tests performed and the resulting requirement for very large sample sizes to achieve statistical significance. In addition, the relationship between the discovered variants or loci and disease pathogenesis is not always obvious.

Genome-wide linkage studies—The first genome-wide approach that was technically feasible to apply in large samples was linkage studies. A requirement of linkage studies is the availability of families with at least two affected relatives (most commonly affected sibling pairs). The basic premise of linkage studies is that the ‘disease locus’ will co-segregate with the disease in families. As a result, regions of the genome that harbor susceptibility loci will be shared among affected relatives more often than expected by chance. For example, using a sibling pair design, one looks for alleles at marker loci that are shared by both siblings more than 50% of the time (the expected amount of allele sharing between siblings). Depending on whether both parents are also genotyped, the precision of the estimate that the genotypes are truly identical by descent (each shared allele inherited from the same parent) or identical by state (same allele but not necessarily inherited from the same parent) varies. The evidence for linkage is reported as a likelihood ratio, or a LOD score (log of the odds in favor of linkage). Linkage studies are performed in many families, and LOD scores are summed across families. Typically LOD scores >>3 (representing greater than 1,000 to 1 odds in favor of linkage), preferably >3.4, are required to declare that an observed linkage to a complex disease is significant.

The advantage of linkage studies is that they require relatively few genetic markers, at least by 21st century standards. Genome-wide linkage studies in the 1990s typically used 400-800 highly polymorphic microsatellite markers (also referred to as short tandem repeat polymorphisms, or STRPs), but today it is easier to use ~8,000-10,000 SNPs, which are available on genotyping arrays and provide equivalent or better coverage and information as 1,000 STRPs (163). Moreover, linkage studies will reveal regions or genes that harbor multiple rare variants that confer risk for disease, even if the specific variant differs among families. This is an often-overlooked advantage of linkage studies, although discovering multiple rare variants that are contributing to a linkage peak is a daunting task. In addition to

the requirement for studying families, the most significant limitations of linkage studies are that it identifies very broad regions that can contain hundreds of genes (i.e., has poor resolution) and has low power to detect risk variants with modest effect sizes on disease risk.

Genome-wide association studies (GWAS)—In contrast to genome-wide linkage studies, the main advantages of GWAS are its excellent resolution, its power to detect risk variants with modest effect sizes, and that it does not require studying families (164). The GWAS extends the candidate gene approach described above to include markers that 'tag' (at least in theory) all common variation in the genome. GWAS became feasible in the past five years as high throughput genotyping platforms, such as those made by Affymetrix or Illumina, with 300,000 to over 1 million SNPs became available and affordable. Moreover, using the data available through the HapMap project (165-168), >3 million genotypes can currently be 'imputed' for subjects from most racial/ethnic groups using the genotypes generated by the Affymetrix or Illumina SNP arrays and the known haplotype structure of the HapMap samples (168-170). Therefore, current GWAS typically test for associations with a million or more SNPs. The statistical burden resulting from performing this many tests requires very stringent thresholds of significance (typically with $p<10^{-7}$) and, therefore, very large sample sizes to achieve genome-wide levels of significance. The latter requirement is one of limitations of this approach and has encouraged many national and international collaborations and meta-analyses, in which results of many smaller GWAS are combined to increase power. Two recent meta-analyses of asthma GWAS in Europe (171) and the U.S. (172) demonstrate the power of this approach (discussed below).

The greatest limitation of the GWAS is that it will primarily detect common risk variants, both because the genotyping platforms include mostly common variants and because of the reduced power to detect associations with SNPs with low (<1%) minor allele frequencies (MAFs). In fact, the GWAS experiences to date, across many diseases including asthma, suggest that the risk alleles identified by this approach account for a very small proportion of the genetic risk. There are many possible explanations for this observation, (see 'Missing Heritability' section below). However, one currently popular explanation for poor predictive power of the risk variants identified by GWAS is that rare variants, which will not be detected by GWAS, have overall larger effects than common variants on disease risk, challenging the 'common disease-common variant hypothesis' (173-175), one of the basic rationales for performing GWAS (164, 176).

Re-sequencing studies—Whereas GWAS have dominated common disease genetic studies in the past five years, sequencing studies will dominate the next five. The current explosion of sequencing studies, most of which are ongoing at the time of this writing, has been facilitated by the development of high throughput, massively parallel sequencing, referred to as Next Generation (NextGen) sequencing (156, 177). The rationale for these studies is the belief that rare variants, with larger effect sizes on disease risk than common variants, explain a significant portion of the genetic risk for common diseases (reviewed in 178, 179). Interestingly, theoretical modeling performed a decade ago suggested that multiple, low frequency alleles at susceptibility loci are more likely than one or a few common alleles to contribute to risk for common diseases (180, 181). Such allelic heterogeneity will not be detected by the classical statistical approaches to association studies, including GWAS. In addition, as mentioned above, the most commonly used genotyping platforms nearly exclusively interrogate common variation. In contrast, the detection of rare variants requires the re-sequencing of genes, exomes, or even whole genomes in large samples of individuals to discover rare variation that is not present or tagged by variation on the genotyping platforms. There are currently many ongoing studies to re-sequence the exomes of hundreds or thousands of individuals to discover rare variants

that are enriched in cases compared to controls, but the jury is still out as to whether rare variants will account for a significant proportion of the genetic risk for complex diseases, including asthma and allergic diseases. However, it is already clear that the cost of sequencing genomes or exomes is dropping so rapidly that this technology may even replace SNP genotyping in the near future. In contrast, the bioinformatic and computational requirements for storage, analysis, and interpreting sequence data are enormous, and developments in this area are barely keeping apace with the generation of these data.

The requirement for replication—Because of the large number of tests performed in genetic studies there is always the possibility that some variants will show very significant associations by chance alone. This is true for candidate gene association studies as well, although to a lesser extent. As a result, the gold standard for validating an association is to replicate the association in at least one independent sample. The replication sample(s) should be of sufficient size to minimize the likelihood of a type 2 error (false negative result), and the replicated association should ideally be with the same allele and in the same direction as in the original study. However, because of the complexity of these diseases, and the likely important roles for early life environmental exposures (see 'Environmental modifiers' section above), negative replication studies of very strong association signals can be difficult to interpret and the evidence for lack of replication should be as carefully evaluated as those supporting the original association (182).

Summary: choice of approach for gene discovery and the role of allele frequency spectrum and effect sizes—The approaches to gene discovery reviewed above have fallen in and out of favor, as the limitations of each approach become more apparent and developing technologies allow us to adopt newer strategies that were previously technically implausible or financially prohibitive. However, we believe that all of these approaches should have a place in the gene mapper's toolbox, because it is unlikely that any one approach will be sufficient to identify all genetic risk factors. The best choice of method, of course, depends on the true underlying genetic architecture of asthma and allergic disease, which is currently unknown (179, 183) (Fig. 1). If, for example, the most important genetic risk factors for asthma and allergy are common variants at many loci with modest effect sizes, then GWAS, and meta-analyses of GWAS, should be a powerful approach for finding these variants. Under that scenario, the variants identified by GWAS should collectively explain most of the genetic risk, or heritability, of the trait. If, however, most of the genetic risk for these diseases is due to multiple rare or low frequency variants with relatively larger effect sizes, then re-sequencing or even linkage studies might be the best or only way to detect these risk variants. In fact, it is likely that the genetic architecture of asthma and allergy encompasses both common and rare alleles, which will be revealed by a combination of approaches. As sequence data become available over the next few years, it will be particularly interesting to see whether genes with common risk alleles (such as those discovered by GWAS) also harbor rare variants that confer risk or whether the genes with common vs. rare risk variants are mutually exclusive. If the latter is the case, it will be additionally interesting to determine whether the genes that harbor rare variation with larger effects on disease risk share any features in common with each other, such as a molecular signatures of positive or negative selection.

An overview of asthma and allergy gene discoveries

Candidate gene association studies

The vast majority of the >100 loci harboring variation that has been associated with risk for asthma and allergic phenotypes were first identified by candidate gene association studies (160-162), starting with the early studies of HLA and allergies in the Blumenthal and Marsh

laboratories in the 1970s (184, 185). As of 2007, variation in more than 30 genes had been associated with asthma or allergic phenotypes in at least five independent (candidate gene) association studies (161, 162). Because these studies have been extensively reviewed elsewhere (160-162), an overview of all genes associated with asthma or allergy are not further discussed here.

Linkage followed by positional candidate studies

Identifying genes via linkage studies proved to be quite challenging. Among the >25 linkage studies reported between 1996 and 2009 (reviewed in 186, 187), only nine genes were successfully identified by positional candidate studies in linked regions (188-196) (Table 3). All but one of these genes (*IRAK3*) were novel at the time, i.e. they had not been considered as asthma 'candidate' genes prior to their identification through linkage and positional cloning studies.

Two recent meta-analyses of asthma and atopy linkage studies combined results for nine (186) and 20 (187) independent populations, providing data for 5,832 individuals of European ancestry in 1,267 pedigrees with asthma diagnoses and 5,425 asthmatic individuals in 2,053 racially and ethnically diverse families, respectively. Genome-wide significant linkages for asthma were reported for regions on 2p21-p14 (187), for asthma or BHR on an overlapping region on 6p22.3-21.1 (186, 187), and for BHR on 2q22.1-q23.3, 7q12.11-q31.1, and 5q23.2-q34 (186). Genome-wide significant linkages for atopy phenotypes were reported on 2q32-q34 for eosinophil count (187), for overlapping regions on 3p25.3-q24 and on 17p12-q25 for positive SPT (186, 187), on 5q23-q33 for a quantitative measure of SPT (187), and on 5q11.2-q14.3 and 6pter-6p22.3 for IgE (186). The region linked to asthma and BHR on 6p includes the HLA region, the location of one of the positionally cloned asthma genes, *HLA-G* (190), and for one of the most significant associations in a European meta-analysis of a GWAS for asthma (*HLA-DQ*) and for IgE (*HLA-DRB1*) (discussed below in 'Meta-analysis of GWAS') (171). The atopy locus on 5q harbors the *ADRB2* gene and another positionally cloned asthma gene, *CYPIP2* (191). The atopy loci on 2q and 3p include many outstanding candidates, including *ICOS*, *CD28*, and *CTLA4* on 2q and *TLR9*, *CCR3*, and *CCR5* on 3p. Curiously, both meta-analyses identified a broad region on chromosome 17 linked to atopy (positive SPT) that includes the 17q21 asthma susceptibility locus (*ORMDL3*/*GSDML*) (197), which does not show associations with atopy (discussed below in 'Genome-wide association studies'). This suggests that at least one additional locus in this region contributes to atopic phenotypes and that the asthma and atopy susceptibility loci in this region are distinct.

In general, linkage studies of asthma and allergy were plagued by poor replication of linkage signals from study to study, possibly due to small sample sizes. Whether the recent meta-analyses of linkage studies provides some clarity on the location of the most important asthma or atopy loci remains to be seen. However, as revealed by the meta-analyses, many of the more modest linkage regions are consistent across studies. Nonetheless, the variants that explained the linkage signals have not yet been identified for most of these regions in families showing linkage. A possible explanation for why the latter step has been so difficult could be the presence of multiple risk variants or even multiple genes within the same linkage peak, with different variants or genes contributing to risk in different families. Because the follow-up studies to linkage are basically association studies of variation under linkage peaks, linkage signals that result from allelic or locus heterogeneity would have been (and still are) difficult to unravel. However, it is noteworthy that variation in many genes located within replicated linked regions, such as those on 6p, 5q, and 12q have been associated with asthma and allergic phenotypes. Although never demonstrated empirically, it is possible that different families are segregating variation in different genes (or different combinations of variation at each gene) in these regions. This would generate linkage

signals that would not be explained by common variation at a single locus. Only direct sequencing of the linked regions in families showing evidence for linkage would allow direct testing of this hypothesis.

Genome-wide association studies

The first GWAS of asthma, published in 2007, identified *ORMDL3* as a novel asthma susceptibility locus on chromosome 17p21 (197). Common variation in this locus was associated with asthma in 1,000 cases and 1,000 controls, and then replicated in >5,000 subjects. Moreover, one of the associated variants was an expression quantitative trait locus (eQTL) for *ORMDL3* in lymphoblastoid cell lines (LCLs) (197), indicating that at least one of the associated SNPs (among many that are in very strong LD) regulates the expression of *ORMDL3* in a genotype specific manner. Subsequent studies showed that the eQTL also regulated expression of a neighboring gene, *GSDML* (also called *GSDMB*) (197-200). In fact, due to the extensive LD between SNPs and the co-regulation of the expression of genes in this region, it has not been possible to delineate between the effects of these two genes and, as a result, this is now referred to as the 17q21 asthma locus. Many studies have since replicated associations with SNPs on 17q21 and asthma, further showing that the association is primarily with childhood onset asthma (199, 201-203) and is more pronounced in children with exacerbations, respiratory viral infections, severe asthma, and exposure to environment tobacco smoke in infancy (199, 201, 204-206). However, variation at this locus is not associated with atopy (171, 199, 201, 203), providing evidence for an asthma susceptibility locus that acts through non-atopic (i.e. non-IgE-mediated) pathways. The functions of *ORMDL3* and *GSDML* are only beginning to be understood (207-209), but how one or both of these genes influence risk for childhood asthma is currently unknown.

This first asthma GWAS was followed by many others of asthma (210-214), atopic dermatitis (215), eosinophilic esophagitis (EoE) (216), atopy (217) and the asthma/allergy intermediate quantitative traits, YKL-40 levels (66), total serum IgE (67), eosinophil count (68), and lung function (FEV_1, FEV_1/FVC) (218). Despite the relatively large sample sizes of the published GWAS [compared to those in the earlier candidate studies (161)], no associations replicated across all studies and few reached genome-wide levels of significance (Table 4A). This is expected if the variants associated with these phenotypes have very small effects on disease risk, thereby requiring even larger samples to detect significant associations. In addition, heterogeneity within each sample could dilute the effects of risk variants if a particular variant confers risk only in some individuals but not in others. In particular, early life environmental exposures may interact with genotype to determine risk so that associations will only be apparent in exposed individuals. Such gene-environment interactions are likely widespread in asthma and allergic diseases, as recently reviewed (219), and variants involved in interactions will be very difficult, if not impossible, to detect in a GWAS.

Meta-analyses of GWAS

To maximize the power to detect risk alleles with modest effect sizes, the results of individual GWAS can be combined in a meta-analysis. Two meta-analyses of asthma GWAS have recently been completed, one by the GABRIEL Consortium (171) and one by the EVE Consortium (172) of European and U.S. investigators, respectively. While the GABRIEL meta-analysis included only subjects of European ancestry, the EVE meta-analysis included racially and ethnically diverse subjects from the U.S. and Mexico. The combined results of these two large meta-analyses yielded a set of highly replicated associations, some of which are evident in ethnically diverse subjects and some that may be ethnic- or race-specific (Table 5). These two meta-analyses are discussed in detail below. Two meta-analyses for lung function (FEV_1 and FEV_1/FVC ratio) have been reported by the

SpiroMeta (69) and CHARGE (70) Consortiums. The results of those studies are summarized in Table 4B but are not discussed in more detail here because, to date, none of the SNPs or genes associated with lung function are also associated with asthma or allergic disease, although some have also been associated with COPD (220).

The GABRIEL Consortium meta-analysis of European asthma GWAS

The GABRIEL Consortium (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) reported the first meta-analysis of asthma GWAS in 10,365 cases and 16,110 controls recruited from 23 studies, and genotyped for 582,892 SNPs (171). This sample included the subjects in the first GWAS that discovered *ORMDL3*/*GSDML* as a novel asthma susceptibility locus (197). In the meta-analysis, SNPs in or near the following six genes reached genome-wide levels of significance ($p \leq 7.2 \times 10^{-8}$): *HLA-DQ*, *ORMDL3*/*GSDML*, *IL33*, *IL18R1*, *IL2RB*, and *SMAD3*; SNPs in or near three additional genes had p-values $\leq 5.0 \times 10^{-7}$: *SLCA22A5*, *IL13*, and *RORA* (Table 5). Associations were generally more significant in childhood onset asthma. This was particularly true for the associations with SNPs at the 17q21 *ORMDL3*/*GSDML* locus, for which there was significant heterogeneity in the ORs between childhood onset and adult onset asthma (smallest p-value for childhood onset asthma = 6.0×10^{-23}, OR 0.76; smallest p-value for adult onset asthma = 0.49). In contrast, the *HLA-DQ* association was more significant in cases with adult onset asthma, although the heterogeneity in the ORs between adult cases ($p = 4.0 \times 10^{-8}$, OR 1.26) and child onset cases ($p = 2 \times 10^{-5}$, OR 1.14) was not significant. There were no significant associations observed for cases with severe asthma or occupational asthma; or for interactions between any of the associated SNPs.

A second GWAS of total serum IgE was conducted in 7,087 cases and 7,667 controls. Significant associations were reported with SNPs in the class II region of the MHC ($p = 8.0 \times 10^{-15}$), which was independent of the asthma association with *HLA-DQ* SNPs. Previously reported associations were replicated with SNPs in or near the *FCER1A*, *IL13*, *STAT6*, and *IL4R*/*IL21R*, although none reached genome-wide levels of significance in the meta-analysis. Surprisingly, there was no overlap between the most significant SNPs associated with asthma and the most significant SNPs associated with total serum IgE, suggesting that asthma and IgE-mediated pathways may be genetically distinct.

The investigators used the seven SNPs associated with childhood asthma to classify individuals with a predicted probability of disease ≥0.5. In this analysis, the sensitivity for classifying subjects as having or not having asthma was only 35%, with specificity of 75%. Thus, although these variants show very significant associations with asthma they are overall poor predictors of disease status, reflecting both their small effect size and common allele frequencies in the population.

The EVE Consortium meta-analysis of asthma GWAS in ethnically diverse populations

The EVE Consortium is a collaboration between U.S. investigators to identify asthma genes in ethnically diverse populations. Nine groups of investigators contributed asthma GWAS results for European Americans (1,486 cases, 1,539 controls, 620 case-parent trios), African American/African Caribbeans (1,154 cases, 1,054 controls, 413 case-parent trios), and Latinos (606 cases, 792 controls, 1,082 case-parent trios), yielding a combined sample of 3,246 cases, 3,385 controls, and 2,115 case-parent trios (172). Meta-analyses were performed within each racial/ethnic group and in the combined sample of racially and ethnically diverse subjects. SNPs with the most significant associations within each group or in the combined sample were genotyped in a replication sample of 7,202 cases, 6,426 controls, and 518 case-parent trios, comprised of European Americans (3,019 cases, 2,511

controls, 69 case-parent trios), African Americans (2,639 cases, 2,292 controls, 11 case-parent trios), and Latinos (1,544 cases, 1,623 controls, 438 case-parent trios). Each sample was genotyped with either an Illumina or Affymetrix array so a common set of approximately 2 million HapMap SNPs were either directly genotyped or imputed in each sample. In these analyses, the threshold for genome-wide significance was $p < 2 \times 10^{-8}$.

The EVE meta-analysis revealed SNPs in or near four loci that met genome-wide criteria for significance: *ORMDL3*/*GSDML* on 17q21, *IL1RL1* on 2q12, and *TSLP* on 5q22.1 in the combined sample, and *RTP2* on 3q27.3 in the Latino sample. SNPs in 11 other regions had p-values $<10^{-6}$, including two potentially ethnic-specific associations in African Americans/African Caribbeans, one in European Americans, and one in Latinos. The most significant SNP in each of these 15 regions was genotyped in the replication samples; two SNPs failed genotyping, one with a potentially European American-specific association and one with potential association in the combined sample. Among the remaining 13 SNPs, those in or near four genes replicated associations with asthma: *IL1RL1* (combined meta+replication $p = 1.5 \times 10^{-15}$), *TSLP* (combined meta+replication $p = 1.0 \times 10^{-14}$), *IL33* (combined meta +replication $p = 1.7 \times 10^{-12}$), and *ORMDL3/GSDML* (combined meta+replication $p = 2.2 \times 10^{-16}$). One additional African American/African Caribbean-specific association replicated in the African American samples: *PYHIN1* on 1q23.1 (combined meta+replication $p = 3.9 \times 10^{-9}$).

Interestingly, among the four pan-ethnic associations, none reached genome-wide levels of significance within any one group. Although SNPs in the *ORMDL3*/*GSDML* region achieved p-values $<10^{-6}$ in the European American and Latino samples (smallest p-value in the African American/African Caribbean sample at this locus was 0.0012), none of the other three replicated regions had SNPs with $p < 10^{-5}$ in any one racial/ethnic group despite sample sizes of 2-3,000 subjects per group. This reflects, at least in part, the modest effects of these common variants on disease risk. In fact, the odds ratios associated with the risk alleles at the four replicated pan-ethnic asthma susceptibility loci ranged from 1.10 (*IL1RL1* in the African Americans/African Caribbeans) to 1.31 (*ORMDL3*/*GSDML* in the African Americans/African Caribbeans).

The association with SNPs in *PHYHIN1* in subjects of African ancestry is quite interesting. The associated SNPs (rs1101999 and rs1102000) are in perfect LD with each other in populations of African descent, in whom minor allele frequencies are approximately 0.35. However, the associated (minor) alleles at these SNPs are absent in European populations. It is possible, therefore, that these associations are truly African-specific due to a common variant that is present primarily in populations of African descent or as a result of admixture (the alleles are present in Latino populations at about 0.02 frequency). Alternatively, there may be other variation in this gene in Europeans that is associated with asthma risk, but not well interrogated on the current genotyping platforms. Future re-sequencing studies of this gene in ethnically diverse cohorts will allow us to address this question and to determine whether *PYHIN1* is a race-specific asthma susceptibility locus.

Summary of meta-analyses of asthma GWAS

Two large meta-analyses of asthma GWAS in European and diverse U.S. populations produced remarkably similar results (Table 5). SNPs in or near seven loci were associated with asthma in both studies, and SNPs in or near four of these loci had p-values at or near genome-wide levels of significance in both studies, with contributions from ethnically diverse samples: the 17q21 locus, the *IL1RL1*/*IL18R1* locus, *TSLP*, and *IL33*. Thus, these four loci can be considered robustly associated asthma susceptibility genes. Moreover, three of these associations highlight the importance of epithelial cell-derived cytokines (TSLP and IL-33) that promote differentiation and activation of T helper (Th) 2 cells and their receptors

(*IL1RL1* encodes ST2, the receptor for IL-33 on mast cells, Th2 cells, T regulatory cells, and macrophages) (221-225). Notably, associations between allergic diseases and variants in or near these three genes had been previously reported. In a GWAS of eosinophil count, SNPs in *IL1RL1* and *IL33* were associated first with eosinophil count and then with asthma (68) and SNPs near *TSLP* were among the most significant in a GWAS of eosinophilic esophagitis (a food allergy-related disorder) (216). Candidate gene studies of *TSLP* (226-229) and *IL1RL1* (202, 230-232) have further implicated these loci in asthma and atopy susceptibility. The combined data from candidate gene studies and GWAS suggest that variation in these three genes influence asthma risk and atopy phenotypes through shared pathways. As discussed above, the SNPs at the 17q21 asthma locus do not show associations with total serum IgE, positive SPT, or allergic diseases. Although the function of 17q21 genes and their role in asthma pathogenesis is currently unknown, one or more of these genes influence asthma risk through non-atopic, and perhaps novel, pathways.

Notably, the asthma-associated SNPs detected in the GABRIEL and EVE meta-analysis have modest effects on risk. The seven most associated SNPs in the GABRIEL meta-analysis (Table 5) could accurately classify individuals with asthma with only 35% sensitivity (with a predictive probability of 0.5, i.e., assuming the model is correct at least 50% of the time) (171). This is also reflected in the small ORs reported in the EVE meta-analysis for the most associated SNPs (172). It is possible that additional asthma-associated risk alleles with main effects will be revealed in future, even larger meta-meta-analyses, but it is unlikely that those as yet undiscovered asthma risk variants will significantly increase the sensitivity of predicting disease status based on genotypes or explain significantly more of the genetic risk for asthma. Importantly, however, these studies have and will continue to highlight the key pathways in asthma disease onset and progression and to identify potential therapeutic targets, which could lead to more effective treatment of asthma. Nonetheless, the GWAS (and meta-analyses of GWAS) experience to date suggests that common variants with significant main effects on asthma risk have only modest effect sizes and account for only a very small proportion of the genetic risk, or heritability, of this common disease. Thus, it is timely to ask questions about the nature of the remaining genetic contributions to asthma risk.

‘Missing heritability’ in asthma and allergic diseases

Despite the successes of GWAS for discovering common risk alleles for many complex diseases and quantitative phenotypes, only a small proportion of the heritability are accounted for by these variants, as is now apparent for asthma. This has been termed the ‘dark matter’ or ‘missing heritability’, which has been discussed extensively in the literature (178, 179, 233-244). Because the genetic architecture of asthma seems similar to other common diseases in this regard, we will review here the potential explanations for these observations, which we will consider in three categories. First, the genotyping platforms typically used for GWAS do not interrogate all variation. Missing from the typical GWAS are rare variants and structural variants, such as copy number variation (CNVs) and indels, which are not tagged or covered by SNPs on the SNP genotyping arrays. The former will only be detected by direct sequencing, and a number of ongoing studies of asthma as well as many other common diseases should shed light on the importance of rare variants in the genetic architecture of these diseases, as discussed above. Structural variation is quite common in the human genome and because these polymorphisms can result in complete deletions or duplications of genes they are a potentially important source of variation to consider in genetic studies of common diseases (245-248). Currently, however, studies of asthma (249, 250) have been limited by the fact that structural variants are poorly represented on the SNP arrays (251), so it is still unknown as to whether structural variants contribute significantly to the genetic architecture of asthma and allergic diseases.

Alternative approaches for comprehensively surveying CNVs and indels are becoming more available and affordable so we should also know the answer to this question in the near future (252-254).

The second source of the 'missing heritability' is genetic risk due to interaction effects. Current GWAS approaches test for associations between each SNP and the disease or phenotype under investigation. As a result, GWAS will be most powerful for detecting SNPs with main effects on disease risk or phenotypic distributions. Testing for gene-gene interactions (i.e. epistasis) in a GWAS is severely hampered by the enormous multiple comparison burden incurred when testing all possible pairs of genes (i.e. for a GWAS using 500,000 SNPs, there are potentially 500,000 × 500,000 or 250 billion interactions to test). Although there are considerable efforts ongoing to develop methods for studying gene-gene interactions using systems biology and network approaches, this area of investigation is still in its infancy and has not yet shed light on whether a significant proportion of the heritability of asthma is due to gene-gene interactions. In contrast, we already know that gene-environment interactions are important determinants of risk for asthma and allergic disease, as recently reviewed (219). Although genome-wide gene-environment interaction studies (GWIS) do not carry the same statistical burden as genome-wide gene-gene interaction studies, they still require very large samples (255). Moreover, very large datasets used for GWAS do not typically have uniformly measured environmental exposure data. Nonetheless, based on the many well-replicated gene-environment interaction effects on risk for asthma and allergic disease (219, 256-258), it is likely that a significant proportion of the missing heritability for these phenotypes will be accounted for by gene-environment interactions.

It is possible that estimates of heritability for many complex phenotypes are inflated. This is particularly true for estimates based on twin studies because monozygotic twins not only share more of their genes [100%, including the sharing of *de novo* mutations (235)] compared to dizygotic twins (~50%), but they also share a more 'identical' environment than do dizygotic twins. In addition, the heritability of any particular trait may vary significantly in different environments (243) and for different phenotypic subgroups (242), all of which are pooled in the large samples required for GWAS studies. As a result, the heritability for the trait under investigation may in fact be much smaller in the samples included in GWAS due to environmental and phenotypic heterogeneity.

Other considerations

In this review, we chose to focus on the current status of genetic linkage and association studies and the light that those studies have shed on the genetic architecture of asthma and allergic phenotypes. We believe that the field is at a critical juncture with respect to moving beyond GWAS to unravel the molecular, cellular, and physiological effects of variation at associated SNPs and characterizing the roles of associated genes in pathogenesis, as proposed by a recent workshop sponsored by the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) (259). We think that such studies are still in their infancy and will, therefore, be the subjects of future reviews on asthma and allergy genetics. We include under this umbrella characterizing the importance of epigenetic modifications on gene expression during development, as a genome modifier in response to environmental exposures, and as a potential mechanism for gene-environment interactions (260-265). From a genetic perspective, it will be particularly important to determine whether any of the risk-association variation discovered through genetic association (or re-sequencing) studies alters epigenetic modifications as its mechanism of affecting disease risk.

We have also neglected the important field of pharmacogenetics (266), although a number of pharmacogenetic examples in asthma can be cited, including the seminal work on genotype at the *ALOX5* locus and response to leukotriene modifiers (267-271) and at the *ADRB2* locus and response to inhaled beta-agonists (272-275). We expect many more examples of pharmacogenetic interactions being reported as GWAS for drug response are completed during the next year. Such studies may open the door for personalized medicine in the care of asthma patients, and will certainly be the focus of future reviews.

Asthma and allergic disease: same disease or shared pathways?

In the introduction of this review, we posed this question. Here we consider whether genetic studies have shed light on the answer. As mentioned above, because the asthma genetics field was so dominated by candidate gene studies in which 'candidates' were selected on their known function, most genes selected for study were based on their roles in the adaptive or innate immune responses in general, or in Th2-mediated responses in particular. Thus, the paradigm of asthma as an 'allergic' disease predominated in genetic circles. Early linkage studies in 'candidate' regions furthered this notion, by reporting linkages to the 11q region harboring the gene encoding the high affinity Fcβ receptor, *FCERB1* (276), and to the 5q region harboring genes encoding Th2 cytokines, including *IL4* and *IL13* (71, 277).

The first key piece of evidence to suggest that genes in non-allergic, non-immune pathways may have important roles in asthma pathogenesis was the report of *ADAM33* as the first positionally cloned asthma/BHR gene (192) (Table 3); associations with variation in this gene have since replicated in many independent studies (reviewed in 161). This gene is expressed in airway smooth muscle cells and is likely involved in smooth muscle and vascular modeling and remodeling (278, 279), although associations with allergic phenotypes have also been reported (161). More recently a large multi-center study of SNPs in 14 candidate genes for wheeze and allergy revealed that very few candidates showed evidence of an association with both asthma symptoms and elevated IgE levels (280), further suggesting that asthma and atopy are not different manifestations of the same disease. The results of the meta-analyses of asthma GWAS further highlighted the importance of non-immune/non-allergy genes as evidenced by the strong and consistent association of SNPs at the 17q21 locus with childhood onset asthma but not with atopy. Recent functional studies of *ORMDL3* have suggested that it might play a role in epithelial cell remodeling (207, 208). Because typically approximately 80% of children with asthma are also atopic or have allergic disease, very large samples are required to delineate associations that are specific to asthma or to atopy. Thus, the demonstration that associations with variation at the 17q21 locus is specific to asthma and not to IgE levels in the GABRIEL Consortium meta-analysis is compelling evidence that this important locus is a primary asthma-susceptibility locus that acts independently of atopic, or IgE-mediated, pathways.

In contrast, the remaining asthma genes that emerged from the meta-analyses of asthma GWAS have also been associated with atopic phenotypes and allergic diseases. As discussed above, variations in the *TSLP*, *IL33*, and *IL1RL1* genes have shown associations with many atopic phenotypes, including eosinophil count, total serum IgE, allergic disease (eosinophilic esophagitis), and atopy. Thus, these data indicate that asthma and allergic phenotypes may result from genetic alterations in a shared pathway of immunoregulation and promotion of Th2 cytokine production by epithelial cell cytokines. It is tempting to speculate that dysregulation of these pathways predisposes individuals toward the subsequent development of a potentially broad spectrum of diseases. Aberrations in other pathways may confer disease specificity. Thus, common alleles at the 17q21 locus and/or *ADAM33* may be specific for the development of asthma, whereas relatively rare variants in the filaggrin gene

(*FLG*) may be specific for atopic dermatitis (281). We predict that additional genes with specificity for upper airway diseases and food allergies, for example, are yet to be identified.

Concluding remarks and future directions

This is an exciting time in the field of asthma and allergy genetics, as a list of well validated susceptibility genes are emerging and defining important biological pathways. As additional GWAS and meta-analyses for asthma and allergic phenotypes are completed, this gene list will expand and our understanding of the common and unique pathways that are dysregulated in individuals with disease will broaden. The great challenges that we now face are to elucidate the effects of associated variation on gene regulation or function and of associated genes on asthma pathogenesis.

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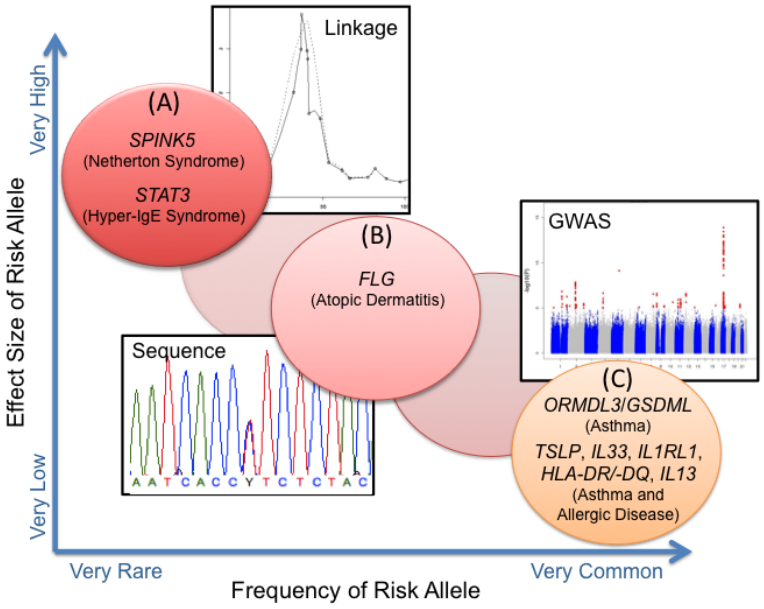

Fig. 1. Genetic architecture of asthma and allergic diseases

Examples are shown for (A) Monogenic diseases with allergic phenotypes that are caused by highly penetrant rare (<1%) mutations. These disease genes can be discovered by linkage studies in families segregating the disease. (B) Complex diseases or phenotypes with low frequency (1-5%) risk alleles with intermediate effect sizes. The relative paucity of genes in his category reflects the limited ability for re-sequencing studies in the past. (C) Complex diseases and phenotypes with common disease risk alleles (>5%) with very low effect sizes and penetrances can be discovered by GWAS. Modified from references (179, 183).

Table 1

Allergic diseases and associated phenotypes that have been considered in genetic studies

Allergic diseases

- Asthma
- Allergic rhinitis (AR)
- Atopic dermatitis (AD)
- Food allergy
- Eosinophilic esophagitis (EoE)
- Urticaria

Clinical or physiological phenotypes

- Severity
- Frequency of exacerbations
- Wheezing in early childhood
- Lung function (FEV_1, FVC, FEV_1/FVC, and PEF)
- Bronchial hyperresponsiveness (BHR)
- Drug response (bronchodilators, inhaled corticosteroids, leukotriene modifiers)
- Age at onset

Atopy-related phenotypes

- Skin prick test
- Allergen-specific IgE
- Total IgE

Trigger-related phenotypes

- Environmental allergens
- Occupational allergens and irritants (e.g., isocyanates)
- Drugs (e.g., aspirin and β-lactams)
- Exercise

Inflammatory phenotypes

- Blood eosinophils and eosinophil cationic protein
- Cytokines
- YKL-40
- Fraction of exhaled nitric oxide (FeNO)

Table 2

Approaches for gene discovery

Approach	Advantages	Disadvantages
Candidate Gene Association Studies (1970's-present)	• Hypothesis-driven • Results easy to interpret • Detects genes with modest effect sizes	• Limited to what we know • Can not discover novel genes or pathways • Requires LD between markers and causal variants
Genome-Wide Linkage Studies (1980's-1990's)	• Genome-wide • Can discover novel genes and pathways • Requires relatively few genetic markers • Does not rely on LD between markers and causal variants • Can detect rare risk variants	• Requires families • Poor resolution • Low power to detect genes with modest effects
Genome-Wide Association Studies (2007-present)	• Genome-wide • Can discover novel genes and pathways • Excellent resolution • Can detect loci with modest effect sizes	• Requires dense marker typing and very large sample sizes • Requires LD between markers and causal variants • Limited to common variants
Re-Sequencing Studies in Genes, Exomes, or Whole Genomes (ongoing)	• Reveals all variation (rare and common)	• Costly • Requires large sample sizes • Computationally and analytically challenging • Difficult to interpret

Table 3

Asthma/atopy genes discovered through linkage and positional cloning studies

Gene	Chromosome Location	Associated Phenotypes	Reference
ADAM33 (a disintegrin and metalloproteinase 33)	20p13	Asthma, BHR	Van Eerdewegh et al. 2002 (192)
DPP10 (dipeptidyl peptidase 10)	2q14	Asthma	Allen et al. 2003 (188)
PHF11 (PHD finger protein 11)	13q14	Asthma, IgE	Zhang et al. 2003 (193)
NPSR1 (neuropeptide S receptor 1) (also called *GPRA*, G protein-coupled protein receptor for asthma susceptibility)	7p14	Asthma, IgE	Laitinen et al. 2004 (189)
HLA-G (human leukocyte antigen G)	6p21	Asthma, BHR, atopy	Nicolae et al. 2005 (190)
CYFIP2 (cytoplasmic FXMR interacting protein 2)	5q33	Atopic asthma	Noguchi et al. 2005 (191)
IRAK3 (interleukin-1 receptor-associated kinase 3) (also called *IRAK-M*)	12q14	Early onset, persistent asthma	Balaci et al. 2007 (194)
COL6A5 (collagen, type VI, alpha 6) (also called *COL29A1*)	3q21	Atopic dermatitis	Söderhäll et al. 2007 (195)
OPN3/CHML (opsin 3/choroideremia-like)	1qter	Atopic asthma	White et al. 2008 (196)

Table 4

Published GWAS and meta-analyses of GWAS for asthma, allergic diseases, or intermediate phenotypes

Phenotype	Study	Gene(s) Discovered	Approx. Size of Discovery Sample	Ethnicity of Discovery Sample	Ethnicity of Replication Sample(s)	Replications
A. GWAS for asthma, allergic diseases, and intermediate quantitative phenotypes.						
Asthma	Moffatt et al. 2007 (197)	*ORMDL3** (17q21)	1,000 cases/1,000 controls	British	German	Replicated association of *ORMDL3* with asthma
YKL-40 levels	Ober et al. 2008 (66)	*CHI3L1**	753 Hutterites	European American	European American, German	Replicated association of *CHI3L1* with YKL-40 levels and asthma
Total serum IgE	Weidinger et al. 2008 (67)	*FCER1A, RAD50, STAT6*	1,530 subjects	German		Replicated associations of *FCER1A, RAD50, STAT6* with IgE; *RAD50* variants associated with AD and asthma
Asthma	Himes et al. 2009 (211)	*PDE4D*	422 cases/1,533 controls from 'Illumina iControlDB'	European American	African American, European American, U.S. Hispanic, British	Replicated association of *PDE4D* with asthma in European Americans
Eosinophil count	Gudbjartsson et al. 2009 (68)	*IL1RL1**, *IKZF2**, *GATA2**, *IL5**, *SH2B3**, *MYB, WDR36, IL33, GRFA2*	9,393 subjects	Icelander	European, European American, Asian	Replicated associations of *IL1RL1, IL33, MYB, WDR36* with asthma in all replication samples
Atopic dermatitis (AD)	Esparza-Gordilla et al. 2009 (215)	*FLG, C11orf30*	939 cases/975 controls; 270 nuclear families	German	German	Replicated association of *C11orf30* with AD
Lung function (FEV_1/FVC ratio)	Wilk et al. 2009 (218)	4q31* (near *HHIP*)	7,691 subjects	European Americans	European Americans	Replicated association of SNP near *HHIP* with FEV_1/FVC
Asthma	Hancock et al. 2010 (210)	*TLE4*	492 asthma case-parent trios	Mexican	Mexican	Replicated association of *TLE4* with asthma
Eosinophilic esophagitis (EoE)	Rothenberg et al. 2010 (216)	*TSLP/WDR36*, 13q31.1*	181 cases/1,974 controls	European American	European American	Replicated association of *TSLP/WDR36* with EoE
Asthma	Mathias et al. 2010 (213)	*ADRA1B, PRNP, DPP10, GNA13*	498 cases/500 controls; 1,028 subjects in 163 families	African American, African Caribbean	African American, European	Replicated association of *DPP10* with asthma

Phenotype	Study	Gene(s) Discovered	Approx. Size of Discovery Sample	Ethnicity of Discovery Sample	Ethnicity of Replication Sample(s)	Replications
A. GWAS for asthma, allergic diseases, and intermediate quantitative phenotypes.						
Asthma	Sleiman et al. 2010 (214)	*DENND1B**, *ORMDL3**	793 cases/1,988 controls	European American	African American. European American, European	Replicated association of *DENND1B* with asthma in European Americans and with opposite allele in African Americans
Asthma	Li et al. 2010 (212)	*RAD50*, *IL13*, *HLA-DR-DQ*, *LRPB1*, *SNX10*, *CA10*, *KCNJ2*	473 cases/1,892 controls from 'Illumina iControlDB'	European		No replication sample included
Atopy	Wan et al. 2011 (217)	*FNDC31**	1,083 cases/2,770 controls	European	European	Association with *FNDC31* not replicated
B. Meta-analyses of asthma and lung function GWAS						
Lung function (FEV_1, FEV_1/FVC)	SpiroMeta Consortium Repapi et al. 2010 (69)	*GSTCD**, *TNS1**, 4q31* (near *HHIP*), *HTR4**, *AGER**, *THSD4**	20,288 subjects	European	European	Replicated associations of *GSTCD*, *TNS1*, and *HTR4* with FEV_1 and *AGER* and *THSD4* with FEV_1/FVC
Lung function (FEV_1, FEV_1/FVC)	CHARGE Consortium Hancock et al. 2010 (70)	*HHIP**, *GRP126**, *ADAM19**, *AGER/PPT2**, *FAM13A**, *PID1**, *HTR4**, *INTS12/ GSTCD/NPNT**	20,890 subjects	European, European American	*in silico* replication in SpiroMeta Consortium	Replicated associations of *HHIP*, *GPR126*, *ADAM19*, *AGER-PPT2*, and *HTR4* with FEV_1 and *INTS12-GSTCD-NPNT* with FEV_1/FVC
Asthma, total serum IgE	GABRIEL Consortium Moffatt et al. 2010 (171)	*IL18R1**, *HLA-DRB1**, *HLA-DQ**, *IL33**, *ORMDL3/ GSDML**, *SMAD3**, *IL2RB**, *SLCA22A5*, *IL13*, *RORA*	10,365 cases/ 16,110 controls	European		No replication sample included
Asthma	EVE Consortium Torgerson et al. 2011 (172)	*ORMDL3/ GSDML**, *IL1RL1**, *TSLP**, *RTP2**, *IL33*, *PYHIN1*	3,601 cases/3,853 controls/1,702 case-parent trios	European American, African American/ African Caribbean, Latino	European American, African American, Latino	Replicated associations of *ORMDL3/GSDML*, *IL1RL1*, *TSLP*, *IL33* in all race/ethnic groups; replicated association of *PYHIN1* in African Americans

Asterisk denotes genes with associations that met criteria for genome-wide significance in each study.

Table 5

Combined results of EVE (172) and GABRIEL (171) meta-analyses of asthma GWAS in European American, African American/African Caribbean, and Latino samples (EVE) and in European samples (GABRIEL).

Gene/Region	EVE	GABRIEL	Race/Ethnic Groups
17q21 (*ORMDL3*/*GSDML)*	1.2×10^{-14}	6.4×10^{-23}*	All
IL1RL1/*IL18R1* (chr. 2)	1.4×10^{-8}	3.4×10^{-9}	All
TSLP (chr. 5)	7.3×10^{-10}	7.52^{-8}	All
IL33 (chr. 9)	2.5×10^{-7}	9.2×10^{-10}	All
SMAD3 (chr. 15)	1.9×10^{-4}	3.9×10^{-9}	Europeans, European Americans
RORA (chr. 15)	2.1×10^{-3}	1.1×10^{-7}	Europeans, European Americans
HLA-DQ (chr. 6)	0.014	7.0×10^{-14}	All
PYHIN1 (chr. 1)	3.6×10^{-7}	--	African Americans/African Caribbeans
IL2RB (chr. 22)	ns	1.1×10^{-8}	Europeans
SLC22A5 (chr. 5)	ns	2.2×10^{-7}	Europeans
IL13 (chr. 5)	ns	1.4×10^{-7}	Europeans

The smallest p-values are shown for SNPs in the most significant genes in either study.

*p-value for association with childhood onset asthma