Published in final edited form as:

Immunol Allergy Clin North Am. 2015 February ; 35(1): 19–44. doi:10.1016/j.iac.2014.09.014.

Genetics of Allergic Diseases

Romina A. Ortiz, MS and **Kathleen C. Barnes, PhD**

The Johns Hopkins Asthma & Allergy Center, 5501 Hopkins Bayview Circle, Room 3A.62, Baltimore, MD 21224, Telephone: 410-550-2071 / Fax: 410-550-2130, kbarnes@jhmi.edu

Abstract

The allergic diseases are complex phenotypes for which a strong genetic basis has been firmly established. Genome-wide association studies (GWAS) has been widely employed in the field of allergic disease, and to date significant associations have been published for nearly 100 asthma genes/loci, in addition to multiple genes/loci for AD, AR and IgE levels, for which the overwhelming number of candidates are novel and have given a new appreciation for the role of innate as well as adaptive immune-response genes in allergic disease. A major outcome of GWAS in allergic disease has been the formation of national and international collaborations leading to consortia meta-analyses, and an appreciation for the specificity of genetic associations to sub-phenotypes of allergic disease. Molecular genetics has undergone a technological revolution, leading to next generation sequencing (NGS) strategies that are increasingly employed to hone in on the causal variants associated with allergic diseases. Unmet needs in the field include the inclusion of ethnically and racially diverse cohorts, and strategies for managing 'big data' that is an outcome of technological advances such as sequencing.

Keywords

allergic disease; genetics; single nucleotide polymorphism (SNP); genome-wide association study (GWAS); next-generation sequencing (NGS); epigenetics; transcriptome

INTRODUCTION

Coca and Cooke were the first to describe asthma, atopic dermatitis (AD), allergic rhinitis (AR), food allergy, and urticaria as 'phenomena of hypersensitiveness' at the annual meeting of the American Association of Immunologists in 1922[1]. Just prior to and following this discourse, there was considerable focus on the relative influence of the environment versus hereditary factors on allergic diseases, with family-based twin and migration studies providing the earliest and most compelling evidence for genetic contributions[2–6]. Studies on the prevalence of allergic traits in relation to family history demonstrated incremental

Disclosure statement: The authors have nothing to disclose

increases in risk of developing asthma, AR, or AD with the presence of one or both parents with allergic disease, and greater than three times the risk if allergic disease occurred in more than one first degree relative[7]. To this date, and despite the dramatic technological advances that have led to the identification of hundreds of genetic variants in genes associated with asthma, AD, and to a lesser degree, food allergy and AR, a positive family history remains one of the most reliable tools for prognosis of allergic disease.

Approaches for disentangling the genetic basis for the allergic diseases have evolved as technological tools for the field of molecular genetics have progressed. With the introduction of the polymerase chain reaction (PCR) in the 1980s, DNA fragments in the human genome could be amplified and then studied for variable fragment lengths of repeats, or 'genetic fingerprinting'. With a catalog of microsatellite markers spanning the human genome, genome-wide linkage studies emerged as a robust approach for identifying genetic hot spots associated with complex traits. Nearly a dozen genome-wide linkage screens were performed on asthma and its associated phenotypes[8–18], for which multiple chromosomal regions provided significant evidence for linkage. From several of these family-based linkage genome-wide screens, six novel asthma genes were identified by positional cloning[18–23]. Similarly, multiple linkage studies were performed for AD (summarized in *Ref.* [24]) and AR[25–29]. It was frequently observed that loci overlapped across associated traits; for example, Daniels and colleagues observed overlapping linkage peaks with quantitative traits associated with asthma including total serum IgE, skin test index, and eosinophil counts, as well as atopy as a qualitative trait[8]. Alternatively, the multiethnic *Collaborative Study on the Genetics of Asthma* reported linkage peaks that were specific to different racial ethnic groups[9].

With the publication of initial efforts in sequencing the human genome[30,31], the opportunity to genotype markers directly in genes of interest was greatly expanded as polymorphisms were identified in the approximately 20,000 to 25,000 genes across the 3 billion chemical base pairs that make up human DNA. Relying upon one of the simplest of these polymorphisms, single nucleotide polymorphisms (SNPs), and relatively simple structural variants, such as insertions/deletions and repeats, this advancement allowed researchers to expand genetic studies beyond linkage toward the genetic association study design. For asthma alone, literally hundreds of candidate genes have been elucidated, and eloquently summarized elsewhere[32–35], representing the relative success of this approach.

The GWAS Era

Following completion of the Human Genome Project, the International HapMap Project[36–38] cataloged genomes representing four biogeographical groups (whites from the United States with northern and western European ancestry; Yorubans from Ibadan, Nigeria [YRI]; Han Chinese from Beijing, China [CHB]; and Japanese from Tokyo, Japan [JPT]) to advance the development of new analytic methods and investigating patterns of genetic variation. Simultaneously, the technological capacity to rapidly (and cheaply) genotype >1M common (>5%) SNPs on thousands of DNA samples from patients phenotyped for various complex clinical traits took the spotlight, and the genome-wide association studies (GWAS) era took off. The content of commercially available GWAS chips grew exponentially with

expansion of the human genome catalog through the Thousand Genomes Project (TGP)[39], and the capacity for discovery of genetic associations has likewise increased with the development of SNP genotype imputation methodologies[40,41], whereby genotyped content from the chip can be combined with the >35M sequenced variants cataloged in the TGP. In the span of only seven years, over 1,924 publications and 13,403 SNPs associated with various complex and quantitative traits[42,43] have been generated by GWAS (Figure 1, **Panel A**).

GWAS has been widely employed in the field of allergic disease. While the precise number of GWAS are difficult to determine, approximately 40 asthma, three atopy, and three AD GWAS (plus a study of >30,000 AD patients genotyped on the Immunochip[44]) have been reported in the *Catalog of Published Genome-Wide Association Studies*[42,43] (Figure 1, **Panel B** and summarized in Table 1). A major outcome of GWAS in allergic disease has been the formation of national and international collaborations leading to consortia meta-analyses, which has greatly facilitated gene discovery owed to the increased power generated from larger sample sizes (which are necessary to detect true associations while adjusting for the multiple comparisons). For example, the first asthma GWAS only showed a significant association between childhood onset asthma and markers near the *ORMDL3* gene on chromosome 17q21 ($P<10^{-12}$) among European populations[45]. When the study was expanded to include >26,000 cases and unaffected controls (*e.g.*, the European-based GABRIEL Consortium[46]), five additional genes plus the 17q locus were strongly associated with asthma[47]. Following completion of 8 U.S.-based, independent asthma GWAS, the NHLBI-supported EVE Consortium was established, comprising >12,000 European American, African American and Hispanic cohorts plus >12,000 independent samples for replication[48]. More recently, the *Transnational Asthma Genetics Consortium* (TAGC) was formed to perform a global meta-analysis for asthma, and to date TAGC includes 67 cohorts representing nearly 20 studies spanning the globe, representing data on over 100,000 asthma cases, controls and family members (Demenais, Nicolae, et al, *unpublished data*).

It can be argued that the huge research efforts and expense committed to GWAS on allergic disease have confirmed suspected genes and pathways, some of which were the focus following linkage study discoveries and a result of the many candidate gene studies undertaken. However, GWAS has, for the most part, generated novel candidate genes and a new appreciation for the role of innate as well as adaptive immune-response genes in allergic disease. In the European-based *GABRIEL Consortium*, six genes were strongly associated with asthma[47], of which three (*IL33*, *ST2*, and the *IKZF3-ZPBP2-GSDMB-ORMDL3* region on chromosome 17q21) were replicated in the *EVE Consortium*[49]. Independent GWAS have provided further support for these same loci[50,51,52]. One of the strongest signals from the combined meta-analysis was for *IL1RL1* (summarized in the Supplementary Figure 11 in *Ref.* [48]), even though the peak SNP differed across ethnic groups. The association between *IL1RL1 SNPs* among African samples was marginal, and might have been overlooked, but in light of evidence for association in other cohorts, *IL1RL1* showed the strongest association overall ($P=1.4\times10^{-8}$).

Lessons learned from candidate gene and positional cloning studies included the specificity of genetic associations to sub-phenotypes of allergic disease. For example, two null

mutations (R501X and 2282del4) in the gene encoding filaggrin (*FLG*) are arguably the most consistently associated polymorphisms with risk of AD, but numerous studies have also implicated a role for these mutations in the development of other atopic diseases, such as asthma and rhinitis, suggesting generalizability of *FLG* mutations to the allergic diathesis. However, it has been argued that the 'atopic march' (*e.g.*, the tendency for AD to precede asthma, food allergy and AR) and the fact that ~70% of severe AD patients also have asthma and AR later in life can account for this overlap[53]. Similar observations have come from GWAS of allergic diseases. For example, the associations with the *ORMDL3* locus has been strongest with childhood asthma[54], and associations between SNPs in *IL1RL1* and *IL33* have been strongest for atopic asthma as opposed to non-atopic asthma[50]. From the GWAS performed total serum IgE levels, there has been relatively little overlap with genes contributing to risk of asthma (Table 1).

The Next Generation of Asthma Genetics

Despite its success, discoveries from GWAS to date have contributed relatively little to our understanding of the specific causal genetic mechanisms underlying allergic disease. For example, the cumulative genetic risk of the variants identified to date for asthma through GWAS (for which, among the allergic diseases, the most GWAS have been performed) is <15%[35]. This is thought to be due, at least in part, to the fact that the most strongly associated SNPs in GWAS are generally not 'directly causal', but most likely tag SNPs in linkage disequilibrium (LD) with the true unobserved disease-causing SNPs. Moreover, the vast proportion of GWAS associations (>85%) involve variants in intergenic or intronic regions[55], which is likely a consequence of the array design; *i.e.*, GWAS arrays are based on tag SNPs for common variants, and coding/exonic variation tends in general to be rare and therefore poorly tagged by a common variant, in contrast to intronic and intergenic regions that have a spectrum of variation that is common. Disappointment in GWAS is compounded by a paradigm shift away from the common disease—common variant hypothesis[56] towards the role of rare variants (unlikely to be identified by GWAS[57]) in non-Mendelian diseases[58], particularly with the appreciation that rare variation constitutes the majority of polymorphisms across human populations[39,59].

Resequencing genes in individuals with well-characterized phenotypes is an alternative approach to assess the contribution that *both* rare and common variants make to disease and overcome the limitations of GWAS. Until recently, Sanger termination sequencing[60] was the only option for interrogating rare variants, but this approach is costly and cannot be done on a large scale. The emergence of massively parallel, second-generation DNA sequencing in 2005[61] has made resequencing an affordable tool to study genetic variation, and in the past several years has been increasingly used either as a targeted approach to follow-up on specific genetic regions or as an unbiased approach towards gene discovery either by whole exome (WES; ~30 Mb total) or whole genome sequencing (WGS)[62]. While rare coding variants may have a greater functional impact than common variants, their analysis must consider the low frequency of any variant since it will reduce the power to infer statistical associations (*i.e.*, insufficient numbers of copies of the rare variant allele in a typical dataset). However, this can be overcome by evaluating the collective frequency of rare, nonsynonymous variants within one or more genes, or for a pathway(s), or the functional

impact of the discovered variations, such as nonsense substitutions, frameshifts, and splice-site disruptions, that have important *a priori* evidence compared to other types of changes (reviewed in *Ref*. [62]).

To date, there are limited examples of the application of NGS technology to identify variants associated with risk of allergic disease, although efforts are underway. A recent example of success combined targeted array-based and in-solution enrichment with the SOLiD sequencing platform to accurately and simultaneously detect 161/170 mutations and deletions associated with primary immunodeficiency (PID) disorders [63]. NGS has also been applied to the study of airway inflammation, including asthma. A study by Leung et al utilized the next-generation sequencing technique called Roche 454 pyrosequencing on peak asthma association signals found in a large consortium-based study in European white subjects and a small group of Chinese children, and found substantial variation in haplotype structures across the populations, thus supporting the notion of potential sequence variations of asthma loci across different ethnic populations [64]. WES has been applied to a small family-based study[65] as well as asthmatics selected at both ends of a phenotype distribution (those with extreme severity phenotypes) [66] with limited success, and a large WGS (>1,000 genomes) on asthma is currently underway[67].

Measuring the Transcriptome in Allergic Disease and its Application to Genetic Studies

Whole genome gene expression profiling, or transcriptomics, is a robust approach towards the quantitative and qualitative characterization of RNA expressed in a biological system. Since the development of synthetic oligonucleotide microarray platforms in 2003[68], transcriptomic profiling has been widely applied in allergic disease. For asthma and its associated traits alone, dozens of studies focusing on whole blood and target cells of the immune system and tissue from the upper and lower airways have been performed using these conventional platforms (reviewed in *Ref*. [69]).

The same robust NGS technology that has recently advanced genetics has similarly transformed transcriptomics. RNA-Sequencing (RNA-Seq) is a more powerful approach to interrogate the transcriptome compared to older microarray technology because of its smaller technical variation[70] and higher correlation with protein expression[71]. RNA-Seq has virtually unlimited dynamic range and permits digital quantification of transcript abundance, assessment of transcript isoforms and alternative splicing[72–74], and it allows for unbiased assembly of transcripts without relying on previous annotation (including non-coding RNAs). To date there are limited examples of applying RNA-Seq technology to allergic disease, but successes include the identification of transcriptomic changes in human airway smooth muscle (ASM) in asthmatics compared to non-asthmatics[75] and the identification of genes differentially expressed in response to glucocorticosteroid exposure (*CRISPLD2*[76], *FAM129A* and *SYNPO2*[77]).

While it is ideal to measure the transcriptome of a primary cell specific to the disease of interest (*i.e*., cells from lung tissue in asthma), this is challenging when considering the large number of samples required given the demands of power. Recently, however, studies have

demonstrated the value of focusing on surrogate target tissues/cells in predicting gene expression in tissues/cells that are challenging to access in large numbers (*i.e.*, lung tissue), which have the potential to significantly move the field forward. For example, Poole and colleagues used whole-transcriptome sequencing (RNA-Seq) to demonstrate that the nasal airway epithelium mirrors the bronchial airway, and subsequent RNA sequencing of candidate airway biomarkers confirmed that children with asthma have an altered nasal airway transcriptome compared to healthy controls, and these changes are reflected by differential expression in the bronchial airway [78].

Differential gene expression in humans is heritable[79,80] and GWAS of gene expression is an innovative approach for mapping functional non-coding variation. Referred to as *expression quantitative trait locus (eQTL) mapping*, this approach is predicated on the notion that abundance of a gene transcript (a quantitative trait) is directly modified by genetic polymorphisms in regulatory elements. The added value of eQTL is the ability to identify disease markers identified in GWAS that are also associated with gene transcripts, and several studies have integrated findings from asthma GWAS with cataloged genome-wide gene expression data[81,82], which can result in a 'gain in power'[83]. Because of limited access to human primary cell types from large populations, many of the human eQTL studies have focused on convenient and immortalized Epstein-Barr virus transformed lymphoblastoid cell lines (LCLs)[84–86], but this approach has had limited success in mapping eQTLs for more than a few of the known asthma genes. In one of the first asthma eQTL studies, SNPs associated with asthma in a subset of the GABRIEL sample were consistently and strongly associated ($P<10^{-22}$) with transcript levels of *ORMDL3*[45]. Hao and colleagues performed an eQTL analysis using lung samples from transplant patients to identify variants affecting gene expression in human lung tissue, then integrated their lung eQTLs with GWAS data from GABRIEL to determine that one of their strongest eQTLs was, similar to the eQTL in LCLs study, a SNP in the chr. 17q21 region[82]. Murphy et al[87] identified common genetic variants influencing expression of 1,585 genes in peripheral blood CD4+ T cells from 200 asthmatics using conventional microarrays, but they acknowledged power was a major limitation. In mining a catalog of 285 published GWAS, however, they identified significant associations with variants in the *ORMDL3* region. When performing tests for association on 6,706 *cis*-acting expression-associated variants (eSNPs) from a genome-wide eQTL survey of $CD4^+$ T cells from asthmatics, the *ORMDL3/GSDMB* locus held up ($P = 2.9 \times 10^{-8}$)[88].

Common Genes in Common Diseases

Several reports have found that allergic diseases such as asthma, rhinitis, conjunctivitis and dermatitis as well as allergic reactions to drugs and foods, are more common in patients with the autoimmune disease systemic lupus erythematosus (SLE)[89–92]. Furthermore, bronchial asthma was found to be the most common cause of cough in a small cohort of SLE patients from Bangladesh[93] and Taiwan[94]. In addition, the inflammatory gene tumor necrosis factor α (TNFα) was found to be a common genetic risk factor for asthma, and autoimmune diseases juvenile rheumatoid arthritis and SLE[95]. In a more recent study, PCR-based genotyping identified four *FCRL3* single nucleotide polymorphisms associated with protection in either juvenile rheumatoid arthritis (JRA) or asthma, but no association was observed with childhood-onset SLE in male Mexican patients. The gene *NRF2* has also been

associated with various immunological pathologies including RA, acute lung injury, asthma, and emphysema[96], among others. There is a long-standing observation of common genetic determinants for both asthma and chronic obstructive pulmonary disease (COPD) identified both through candidate gene studies as well as GWAS[97,98]. Recently, Hardin and colleagues performed a GWAS focusing specifically on patients from the COPD Gene Study with both asthma and COPD, referred to as the COPD-asthma overlap syndrome, and identified associations with variants in genes (*i.e.*, *GPR65*) unique to this sub-phenotype[99]. Finally, there is a large body of research associated with the 'hygiene hypothesis'[100] addressing the potential *beneficial* role of microbial exposures for later development of asthma and allergies. Specifically, the underlying immunological mechanisms and the type of infectious/microbial stimuli relevant to helminth infection (*i.e.*, schistosomiasis) are the same mechanisms that promote the Th2-mediated response in allergic disease[101,102], and common genetic mechanisms underlie both schistosomiasis and asthma have been reported from linkage and candidate gene studies[102].

Other Omics and Allergic Disease

"Omics" refers to an experimental design in which large-scale datasets are acquired from a complete class of biomolecules with the aim of identifying the functional or pathological mechanisms of disease[103]. Such data-dense technologies include: (1) DNA in the context of complete genomics; (2) gene regulation technologies (epigenomics); (3) global protein and/or post-transcriptional modifications (proteomics); and (4) all cellular metabolites (metabolomics) [104].

Transcriptomics extended to microRNA is another burgeoning field. Several miRNAs have been identified as distinct profiles for the development and status of asthma, as well as other allergic phenotypes[105,106]. Approximately 200 miRNAs are known to be altered in steroid naïve asthmatics, establishing a link between abnormal miRNA expression in asthmatic patients and inflammation[107–109]. High-throughput data combined with sequence-based miRNA predictions have been successfully applied[110–114], and more recently, a transcriptome study on miRNA-long non coding RNA interactions suggests better understanding of lung disease regulation and progression[115]. NGS has been utilized to study microRNA expression and interactions with the phosphoinositide 3-kinase (PI3K) pathway in primary human airway smooth muscle (HASM) cells[116].

Concordance rates for asthma and allergies of only ~50% among monozygotic twins suggest differences in exposure to environmental triggers are critical in disease expression[2,117,118], and it has been demonstrated that genes and environmental factors contribute equally to asthma and its associated traits such as tIgE[3]. Similar to the other allergic diseases, the prevalence of asthma has increased dramatically within the 2–3 decades in relation to the deterioration of the environment, favoring a significant contribution of environmental factors[119]. Added to this complexity is the observation that associations with alleles at candidate genes and interactions between these genes might only be observed among certain subpopulations despite nearly identical environmental exposures and similar genetic backgrounds. For example, the *CD14*(-260)C>T variant was associated with low tIgE in school children living in urban/suburban Tucson, AZ[120], but the opposite

association was reported in a farming community[121]. Alternatively, it has been shown that this same variant depends on the *dose* of endotoxin from household dust among African-ancestry asthmatics living in the tropics[122], suggesting the role of endotoxin in allergic disease may be due to the combination of susceptibility genes and exposure. A large body of evidence implicates *in utero* and early life environmental tobacco smoke (ETS) exposure leads to impaired lung function and increased risk of asthma[123–126], and ETS exposure increases strength of the association between markers in candidate genes and atopic asthma[127–129]. Indeed, environmental exposures such as smoking, air pollution and stress have been shown to cause changes in epigenetic modifications of genes as well as altered microRNA expression [130].

Immune responses in allergic disease are dominantly initiated by the release of cytokines such as interleukin-4 (IL4), IL5 and IL13, which activate type 2 helper T cells (TH2) resulting in a decrease of TH1 cytokines and impaired regulatory T cell function, and up or down regulation of DNA methylation on Th-1/Th-2 cytokine genes may affect the sensitization of experimental asthma[131]. In addition, epigenetic changes in immune cells such as T cells, B cells, mast cells and dendritic cells exposed to environmental factors have also been shown to be associated with asthma[132]. A recent study found that DNA methylation in the β-2 adrenergic receptor (*ADRB2*) gene is associated with decreased asthma severity[133]. In addition, an asthma mouse model found that microRNAs targeted genes involved in inflammatory responses and tissue remodeling, and demethylation status in the promoter of the IFN-γ changed in response to chronic antigen sensitization[134].

Environmental stimuli have been shown to directly influence epigenetic modifications, and thus epigenetic regulation may play a role in immune-mediated lung diseases like asthma. Epigenetic regulation maintains tolerance to self-antigens. Thus, abnormal epigenetic activity may lead to a deregulated immune response and thus an immune disorder[135]. Epigenomics allows for the study of gene regulation at the chromosomal level using DNA methylation and CHIP technologies. As an example, 870 genes are differentially methylated in idiopathic pulmonary fibrosis (*IPF*) tissues[136], and changes in miRNAs and fibroblast signature for genes are known to regulate the extracellular matrix in IPF[137,138]. While methylation decreases gene expression, acetylation of histones relaxes chromatin facilitating gene transcription and increasing expression. A recent study has implicated histone modifications in the decrease of *Fas* expression as well as resistance to apoptosis in fibrotic lung fibroblasts[139].

A novel example of this technology is a study in which methylated DNA immunoprecipitation-next generation sequencing (MeDIP-seq) on lung tissue DNA from saline and house dust mite (HDM)-exposed mice was performed and researchers found that chronic exposure to HDM increased airway reactivity and inflammation, as interpreted through increases in IL-4, IL-5 and serum IgE levels, resulting in structural remodeling and hyperresponsiveness consistent with allergic disease. In addition, mice that received HDM exposure had global changes in methylation and hydroxymethylation of approximately 213 genes, with *TGFβ2* and *SMAD3* having the most connected network[140]. These findings demonstrate how allergen exposure could trigger epigenetic changes in the lung genome.

Clinical Implications & Personalized Medicine

Arguably the ultimate goal of genetic studies of allergic disease is to better match individualized treatments to specific genotypes to improve therapeutic outcomes and minimize side effects. For example, despite the relative success of conventional asthma therapies such as inhaled beta agonists and glucocorticoids, most cause adverse side effects[141–143] and a subset of asthmatics are refractory to anti-asthma therapies resulting in significant morbidity as well as a significant financial burden[144–146]. Genetic variation determines drug response through various mechanisms including pharmacodynamics mechanisms, which determine drug metabolism[147].

Recent GWAS and studies of candidate genes related to the β2-adrenergic receptor pathway have attempted to identify specific variants associated with the response to inhaled beta agonists[148–150]. The Arg^{16} allele in *ADRB2* has been associated with greater post-bronchodilator FEV1 response to SABA asthma therapy in asthmatic children[151,152], while the Gly^{16} variant has been associated with changes in peak flow rate (PEFR)[153–155]. In contrast, the Arg^{16} allele has been associated with worsening asthma symptom scores with LABA therapy compared to Gly^{16} homozygotes [156]. Other studies show no difference between the *ADRB2* alleles and asthma symptoms after LABA therapy [157,158]. Further pharmacogenetic studies may achieve a more definitive characterization of the role of $Gly^{16}Arg$ after beta agonist exposure and determine whether receptor kinetics or pro inflammatory effects play a role in the contrasting effects of the genotypes. Additional candidate genes found to be associated with altered beta agonist response in asthmatic children include *ADCY9* [150] and *ARG1* [159] with FEV1 change, and *CRH2* [148] and *SPATS2L* [149] with bronchodilator response. Additional candidate gene studies have also demonstrated altered asthma phenotypes in response to glucocorticoid therapies including *CRH1* [160], *STIP1* [161], *TBX21* [162,163], *ADCY9*[150] [164], and *ORDML3* [165].

Future Considerations/Summary

While GWAS has yielded promising results in the field of allergic disease, association does not imply biological functionality, and follow-up studies are needed to translate initial findings into the biological insights that ultimately will advance prognostics, diagnostics and therapeutics. While the vast amount of genomic data that is now available for a plethora of complex diseases, including allergic disease, has certainly facilitated follow-up association analyses to explore new hypotheses, meta-analyses, and replication of novel findings[166], the scientific community is facing a ‘big data’ crisis[167], as the size of genomic data sets today has begun to overwhelm the existing infrastructure and resources that allow researchers to share or use these data. For the genetics of allergic diseases specifically, there is increasing awareness of the need to design studies that are more inclusive of racially and ethnically diverse study participants[168]. Consider that, in the field of pharmacogenetics, it has been clearly demonstrated that, as an example, African American asthmatics have an increased likelihood for treatment failures and overall differential response to treatment that may be caused by genetic variants specific to their ancestry [169,170]. Each of these needs will undoubtedly be addressed as clinicians and scientists in the field continue to move in a direction of collaboration and an appreciation for a multi-disciplinary approach, attributes

that have already pushed the genetics of allergic disease into the genomic revolution, with promises of improved outcome for the patient.

Acknowledgements

KCB was supported in part by the Mary Beryl Patch Turnbull Scholar Program. RAO was supported by NHLBI Diversity Supplement 3R01HL104608-02S1. The authors are grateful for technical assistance from Pat Oldewurtel and Joseph Potee.

References

1. Coca AF, Cooke RA. On the classification of the phenomena of hypersensitiveness. Journal of Immunology. 1923; 8:163–171.
2. Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD. Genetics of asthma and hay fever in Australian twins. American Review of Respiratory Disease. 1990; 142:1351–1358. [PubMed: 2252253]
3. Palmer LJ, Burton PR, James AL, Musk AW, Cookson WO. Familial aggregation and heritability of asthma-associated quantitative traits in a population-based sample of nuclear families. European Journal of Human Genetics. 2000 Nov; 8(11):853–860. [PubMed: 11093275]
4. Manolio TA, Barnes KC, Beaty TH, Levett PN, Naidu RP, Wilson AF. Sex differences in heritability of sensitization to Blomia tropicalis in asthma using regression of offspring on midparent (ROMP) methods. Human Genetics. 2003 Oct; 113(5):437–446. [PubMed: 12928863]
5. Davis LR, Marten RH, Sarkany I. Atopic eczema in European and Negro West Indian infants in London. British Journal of Dermatology. 1961; 73:410–414. [PubMed: 13883941]
6. Cooke RA, VanderVeer VA. Human sensitisation. Journal of Immunology. 1916; 1:201–205.
7. Dold S, Wjst M, Mutius Ev, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. Archives of Disease in Childhood. 1992; 67:1018–1022. [PubMed: 1520004]
8. Daniels SE, Bhattacharrya S, James A, et al. A genome-wide search for quantitative trait loci underlying asthma. Nature. 1996; 383:247–250. [PubMed: 8805698]
9. CSGA. The Collaborative Study on the Genetics of Asthma: A genome-wide search for asthma susceptibility loci in ethnically diverse populations. Nature Genetics. 1997; 15(4):389–392. [PubMed: 9090385]
10. Ober C, Cox NJ, Abney M, et al. Genome-wide search for asthma susceptibility loci in a founder population. The Collaborative Study on the Genetics of Asthma. Human Molecular Genetics. 1998 Sep; 7(9):1393–1398. [PubMed: 9700192]
11. Malerba G, Trabetti E, Patuzzo C, et al. Candidate genes and a genome-wide search in Italian families with atopic asthmatic children. Clinical and Experimental Allergy. 1999 Dec; 29(Suppl 4):27–30. [PubMed: 10641562]
12. Wjst M, Fischer G, Immervoll T, et al. A genome-wide search for linkage to asthma. German Asthma Genetics Group. Genomics. 1999 May 15; 58(1):1–18. [PubMed: 10333435]
13. Dizier MH, Besse-Schmittler C, Guilloud-Bataille M, et al. Genome screen for asthma and related phenotypes in the French EGEA study. American Journal of Respiratory and Critical Care Medicine. 2000 Nov; 162(5):1812–1818. [PubMed: 11069818]
14. Ober C, Tsalenko A, Parry R, Cox NJ. A second-generation genomewide screen for asthma-susceptibility alleles in a founder population. American Journal of Human Genetics. 2000 Nov; 67(5):1154–1162. [PubMed: 11022011]
15. Yokouchi Y, Nukaga Y, Shibasaki M, et al. Significant evidence for linkage of mite-sensitive childhood asthma to chromosome 5q31-q33 near the interleukin 12 B locus by a genome-wide search in Japanese families. Genomics. 2000 Jun 1; 66(2):152–160. [PubMed: 10860660]
16. Laitinen T, Daly MJ, Rioux JD, et al. A susceptibility locus for asthma-related traits on chromosome 7 revealed by genome-wide scan in a founder population. Nature Genetics. 2001 May; 28(1):87–91. [PubMed: 11326283]
17. Hakonarson H, Bjornsdottir US, Halapi E, et al. A Major Susceptibility Gene for Asthma Maps to Chromosome 14q24. American Journal of Human Genetics. 2002 Jul 15.71(3)

18. Van Eerdewegh P, Little RD, Dupuis J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature. 2002 Jul 25; 418(6896):426–430. [PubMed: 12110844]
19. Allen M, Heinzmann A, Noguchi E, et al. Positional cloning of a novel gene influencing asthma from chromosome 2q14. Nature Genetics. 2003 Nov; 35(3):258–263. [PubMed: 14566338]
20. Laitinen T, Polvi A, Rydman P, et al. Characterization of a common susceptibility locus for asthma-related traits. Science. 2004 Apr 9; 304(5668):300–304. [PubMed: 15073379]
21. Nicolae D, Cox NJ, Lester LA, et al. Fine mapping and positional candidate studies identify HLA-G as an asthma susceptibility gene on chromosome 6p21. American Journal of Human Genetics. 2005; 76:349–357. [PubMed: 15611928]
22. Noguchi E, Yokouchi Y, Zhang J, et al. Positional identification of an asthma susceptibility gene on human chromosome 5q33. Am J Respir Crit Care Med. 2005 Jul 15; 172(2):183–188. [PubMed: 15879417]
23. Zhang Y, Leaves NI, Anderson GG, et al. Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. Nature Genetics. 2003 Jun; 34(2):181–186. [PubMed: 12754510]
24. Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. J Allergy Clin Immunol. 2009 Jan; 125(1):16–29. e11-11; quiz 30-11. [PubMed: 20109730]
25. Haagerup A, Bjerke T, Schoitz PO, Binderup HG, Dahl R, Kruse TA. Allergic rhinitis - a total genome-scan for susceptibility genes suggests a locus on chromosome 4q24-q27. European Journal of Human Genetics. 2001 Dec; 9(12):945–952. [PubMed: 11840197]
26. Yokouchi Y, Shibasaki M, Noguchi E, et al. A genome-wide linkage analysis of orchard grass-sensitive childhood seasonal allergic rhinitis in Japanese families. Genes and Immunity. 2002 Feb; 3(1):9–13. [PubMed: 11857054]
27. Kurz T, Altmueller J, Strauch K, et al. A genome-wide screen on the genetics of atopy in a multiethnic European population reveals a major atopy locus on chromosome 3q21.3. Allergy. 2005 Feb; 60(2):192–199. [PubMed: 15647040]
28. Dizier MH, Bouzigon E, Guilloud-Bataille M, et al. Genome screen in the French EGEA study: detection of linked regions shared or not shared by allergic rhinitis and asthma. Genes Immun. 2005 Mar; 6(2):95–102. [PubMed: 15674395]
29. Kruse LV, Nyegaard M, Christensen U, et al. A genome-wide search for linkage to allergic rhinitis in Danish sib-pair families. Eur J Hum Genet. 2012 Sep; 20(9):965–972. [PubMed: 22419170]
30. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science. 2001 Feb 16; 291(5507):1304–1351. [PubMed: 11181995]
31. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15; 409(6822):860–921. [PubMed: 11237011]
32. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun. 2006 Mar; 7(2):95–100. [PubMed: 16395390]
33. Vercelli D. Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol. 2008 Mar; 8(3):169–182. [PubMed: 18301422]
34. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev. 2011 Jul; 242(1):10–30. [PubMed: 21682736]
35. Mathias RA. Introduction to genetics and genomics in asthma: genetics of asthma. Adv Exp Med Biol. 2014; 795:125–155. [PubMed: 24162907]
36. The International HapMap Consortium. The International HapMap Project. Nature. 2003 Dec 18; 426(6968):789–796. [PubMed: 14685227]
37. International HapMap Consortium. A haplotype map of the human genome. Nature. 2005 Oct 27; 437(7063):1299–1320. [PubMed: 16255080]
38. Thorisson GA, Smith AV, Krishnan L, Stein LD. The International HapMap Project Web site. Genome Res. 2005 Nov; 15(11):1592–1593. [PubMed: 16251469]
39. Abecasis GR, Auton A, Brooks LD, et al. An integrated map of genetic variation from 1,092 human genomes. Nature. 2012 Nov 1; 491(7422):56–65. [PubMed: 23128226]
40. Minimac. http://genome.sph.umich.edu/wiki/Minimac

41. Auer PL, Johnsen JM, Johnson AD, et al. Imputation of exome sequence variants into population-based samples and blood-cell-trait-associated loci in African Americans: NHLBI GO Exome Sequencing Project. Am J Hum Genet. 2012 Nov 2; 91(5):794–808. [PubMed: 23103231]
42. A catalog of published genome-wide association studies [computer program].
43. Welter D, Macarthur J, Morales J, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res. 2014 Jan 1; 42(1):D1001–D1006. [PubMed: 24316577]
44. Trynka G, Hunt KA, Bockett NA, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nat Genet. 2011 Dec; 43(12):1193–1201. [PubMed: 22057235]
45. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression are determinants of susceptibility to childhood asthma. Nature. 2007; 448(7152):470–473. [PubMed: 17611496]
46. GABRIEL. A GABRIEL Consortium Large-Scale Genome-Wide Association Study of Asthma. http://www.cng.fr/gabriel/index.html
47. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010 Sep 23; 363(13):1211–1221. [PubMed: 20860503]
48. Torgerson D. Meta-analysis of Genome-wide Association Studies of Asthma in Ethnically Diverse North American Populations. 2011
49. Torgerson DG, Ampleford EJ, Chiu GY, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet. 2011 Sep; 43(9):887–892. [PubMed: 21804549]
50. Gudbjartsson DF, Bjornsdottir US, Halapi E, et al. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. Nat Genet. 2009 Mar; 41(3):342–347. [PubMed: 19198610]
51. Ferreira MA, McRae AF, Medland SE, et al. Association between ORMDL3, IL1RL1 and a deletion on chromosome 17q21 with asthma risk in Australia. Eur J Hum Genet. 2010 Dec 8.
52. Ferreira MA, Matheson MC, Duffy DL, et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. Lancet. 2011 Sep 10; 378(9795):1006–1014. [PubMed: 21907864]
53. Weidinger S, O'Sullivan M, Illig T, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. J Allergy Clin Immunol. 2008 May; 121(5):1203–1209. e1201. [PubMed: 18396323]
54. Ono JG, Worgall TS, Worgall S. 17q21 locus and ORMDL3: an increased risk for childhood asthma. Pediatr Res. 2014 Jan; 75(1–2):165–170. [PubMed: 24165737]
55. Brown CD, Mangravite LM, Engelhardt BE. Integrative modeling of eQTLs and cis-regulatory elements suggests mechanisms underlying cell type specificity of eQTLs. PLoS Genet. 2013; 9(8):e1003649. [PubMed: 23935528]
56. Reich DE, Lander ES. On the allelic spectrum of human disease. Trends Genet. 2001 Sep; 17(9):502–510. [PubMed: 11525833]
57. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009 Oct 8; 461(7265):747–753. [PubMed: 19812666]
58. Gorlov IP, Gorlova OY, Frazier ML, Spitz MR, Amos CI. Evolutionary evidence of the effect of rare variants on disease etiology. Clin Genet. 2011 Mar; 79(3):199–206. [PubMed: 20831747]
59. Marth GT, Yu F, Indap AR, et al. The functional spectrum of low-frequency coding variation. Genome Biol. 2011; 12(9):R84. [PubMed: 21917140]
60. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A. 1977 Dec; 74(12):5463–5467. [PubMed: 271968]
61. Shendure J, Porreca GJ, Reppas NB, et al. Accurate multiplex polony sequencing of an evolved bacterial genome. Science. 2005 Sep 9; 309(5741):1728–1732. [PubMed: 16081699]
62. Panoutsopoulou K, Tachmazidou I, Zeggini E. In search of low-frequency and rare variants affecting complex traits. Hum Mol Genet. 2013 Oct 15; 22(R1):R16–R21. [PubMed: 23922232]
63. Nijman IJ, van Montfrans JM, Hoogstraat M, et al. Targeted next-generation sequencing: a novel diagnostic tool for primary immunodeficiencies. The Journal of allergy and clinical immunology. 2014 Feb; 133(2):529–534. [PubMed: 24139496]

64. Leung TF, Ko FW, Sy HY, Tsui SK, Wong GW. Differences in asthma genetics between Chinese and other populations. The Journal of allergy and clinical immunology. 2014 Jan; 133(1):42–48. [PubMed: 24188974]

65. DeWan AT, Egan KB, Hellenbrand K, et al. Whole-exome sequencing of a pedigree segregating asthma. BMC Med Genet. 2012; 13:95. [PubMed: 23046476]

66. Fu W, O'Connor TD, Jun G, et al. Analysis of 6,515 exomes reveals the recent origin of most human protein-coding variants. Nature. 2013 Jan 10; 493(7431):216–220. [PubMed: 23201682]

67. Mathias RA, Huang L, O'Connor TD, et al. Patterns of genetic variation in populations of African ancestry observed in whole genome sequencing of 691 individuals from CAAPA. American Journal of Human Genetics. 2013 Abst 1966F.

68. Shaikh TH. Oligonucleotide arrays for high-resolution analysis of copy number alteration in mental retardation/multiple congenital anomalies. Genetics in medicine : official journal of the American College of Medical Genetics. 2007 Sep; 9(9):617–625. [PubMed: 17873650]

69. Sordillo J, Raby BA. Gene expression profiling in asthma. Adv Exp Med Biol. 2014; 795:157–181. [PubMed: 24162908]

70. Marioni JC, Mason CE, Mane SM, Stephens M, Gilad Y. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. Genome Res. 2008 Sep; 18(9):1509–1517. [PubMed: 18550803]

71. Fu X, Fu N, Guo S, et al. Estimating accuracy of RNA-Seq and microarrays with proteomics. BMC Genomics. 2009; 10:161. [PubMed: 19371429]

72. Cullum R, Alder O, Hoodless PA. The next generation: using new sequencing technologies to analyse gene regulation. Respirology. 2011 Feb; 16(2):210–222. [PubMed: 21077988]

73. Cloonan N, Grimmond SM. Transcriptome content and dynamics at single-nucleotide resolution. Genome Biol. 2008; 9(9):234. [PubMed: 18828881]

74. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. Nature reviews. Genetics. 2009 Jan; 10(1):57–63.

75. Yick CY, Zwinderman AH, Kunst PW, et al. Gene expression profiling of laser microdissected airway smooth muscle tissue in asthma and atopy. Allergy. 2014 May 30.

76. Himes BE, Jiang X, Wagner P, et al. RNA-Seq Transcriptome Profiling Identifies CRISPLD2 as a Glucocorticoid Responsive Gene that Modulates Cytokine Function in Airway Smooth Muscle Cells. PloS one. 2014; 9(6):e99625. [PubMed: 24926665]

77. Yick CY, Zwinderman AH, Kunst PW, et al. Glucocorticoid-induced changes in gene expression of airway smooth muscle in patients with asthma. American journal of respiratory and critical care medicine. 2013 May 15; 187(10):1076–1084. [PubMed: 23491407]

78. Poole A, Urbanek C, Eng C, et al. Dissecting childhood asthma with nasal transcriptomics distinguishes subphenotypes of disease. The Journal of allergy and clinical immunology. 2014 Mar; 133(3):670–678. e612. [PubMed: 24495433]

79. Schadt EE, Monks SA, Drake TA, et al. Genetics of gene expression surveyed in maize, mouse and man. Nature. 2003 Mar 20; 422(6929):297–302. [PubMed: 12646919]

80. Cheung VG, Spielman RS. Genetics of human gene expression: mapping DNA variants that influence gene expression. Nat Rev Genet. 2009 Sep; 10(9):595–604. [PubMed: 19636342]

81. Li B, Leal SM. Methods for detecting associations with rare variants for common diseases: application to analysis of sequence data. Am J Hum Genet. 2008 Sep; 83(3):311–321. [PubMed: 18691683]

82. Hao K, Bosse Y, Nickle DC, et al. Lung eQTLs to help reveal the molecular underpinnings of asthma. PLoS Genet. 2012; 8(11):e1003029. [PubMed: 23209423]

83. Li L, Kabesch M, Bouzigon E, et al. Using eQTL weights to improve power for genome-wide association studies: a genetic study of childhood asthma. Front Genet. 2013; 4:103. [PubMed: 23755072]

84. Dixon AL, Liang L, Moffatt MF, et al. A genome-wide association study of global gene expression. Nat Genet. 2007 Oct; 39(10):1202–1207. [PubMed: 17873877]

85. Stranger BE, Nica AC, Forrest MS, et al. Population genomics of human gene expression. Nat Genet. 2007 Oct; 39(10):1217–1224. [PubMed: 17873874]

86. Min JL, Taylor JM, Richards JB, et al. The use of genome-wide eQTL associations in lymphoblastoid cell lines to identify novel genetic pathways involved in complex traits. PLoS ONE. 2011; 6(7):e22070. [PubMed: 21789213]

87. Murphy A, Chu JH, Xu M, et al. Mapping of numerous disease-associated expression polymorphisms in primary peripheral blood CD4+ lymphocytes. Hum Mol Genet. 2010 Dec 1; 19(23):4745–4757. [PubMed: 20833654]

88. Sharma S, Zhou X, Thibault DM, et al. A genome-wide survey of CD4 lymphocyte regulatory genetic variants identifies novel asthma genes. J Allergy Clin Immunol. 2014 Jun 13.

89. Goldman JA, Klimek GA, Ali R. Allergy in systemic lupus erythematosus. IgE levels and reaginic phenomenon. Arthritis and rheumatism. 1976 Jul-Aug;19(4):669–676. [PubMed: 942498]

90. Diumenjo MS, Lisanti M, Valles R, Rivero I. [Allergic manifestations of systemic lupus erythematosus]. Allergologia et immunopathologia. 1985 Jul-Aug;13(4):323–326. [PubMed: 4083230]

91. Sequeira JF, Cesic D, Keser G, et al. Allergic disorders in systemic lupus erythematosus. Lupus. 1993 Jun; 2(3):187–191. [PubMed: 8369810]

92. Shahar E, Lorber M. Allergy and SLE: common and variable. Israel journal of medical sciences. 1997 Feb; 33(2):147–149. [PubMed: 9254878]

93. Azad AK, Islam N, Islam MA, Islam MS, Barua R, Haq SA. Cough in systemic lupus erythematosus. Mymensingh medical journal : MMJ. 2013 Apr; 22(2):300–307. [PubMed: 23715352]

94. Shen TC, Tu CY, Lin CL, Wei CC, Li YF. Increased risk of asthma in patients with systemic lupus erythematosus. American journal of respiratory and critical care medicine. 2014 Feb 15; 189(4): 496–499. [PubMed: 24528323]

95. Jimenez-Morales S, Velazquez-Cruz R, Ramirez-Bello J, et al. Tumor necrosis factor-alpha is a common genetic risk factor for asthma, juvenile rheumatoid arthritis, and systemic lupus erythematosus in a Mexican pediatric population. Human immunology. 2009 Apr; 70(4):251–256. [PubMed: 19480843]

96. Rangasamy T, Guo J, Mitzner WA, et al. Disruption of Nrf2 enhances susceptibility to severe airway inflammation and asthma in mice. The Journal of experimental medicine. 2005 Jul 4; 202(1):47–59. [PubMed: 15998787]

97. Postma DS, Kerkhof M, Boezen HM, Koppelman GH. Asthma and chronic obstructive pulmonary disease: common genes, common environments? Am J Respir Crit Care Med. 2011 Jun 15; 183(12):1588–1594. [PubMed: 21297068]

98. Yao TC, Du G, Han L, et al. Genome-wide association study of lung function phenotypes in a founder population. J Allergy Clin Immunol. 2013 Aug 6.

99. Hardin M, Cho M, McDonald ML, et al. The clinical and genetic features of COPD-asthma overlap syndrome. Eur Respir J. 2014 May 29.

100. Strachan DP. Hay fever, hygiene, and household size. British Medical Journal. 1989 Nov 18; 299(6710):1259–1260. [PubMed: 2513902]

101. Pearce EJ, MacDonald AS. The immunobiology of schistosomiasis. Nat Rev Immunol. 2002 Jul; 2(7):499–511. [PubMed: 12094224]

102. Barnes KC, Grant AV, Gao P. A review of the genetic epidemiology of resistance to parasitic disease and atopic asthma: common variants for common phenotypes? Curr Opin Allergy Clin Immunol. 2005 Oct; 5(5):379–385. [PubMed: 16131910]

103. Wheelock CE, Goss VM, Balgoma D, et al. Application of ‘omics technologies to biomarker discovery in inflammatory lung diseases. The European respiratory journal. 2013 Sep; 42(3): 802–825. [PubMed: 23397306]

104. Derks KW, Hoeijmakers JH, Pothof J. The DNA damage response: The omics era and its impact. DNA repair. 2014 Apr 29.

105. Donaldson A, Natanek SA, Lewis A, et al. Increased skeletal muscle-specific microRNA in the blood of patients with COPD. Thorax. 2013 Dec; 68(12):1140–1149. [PubMed: 23814167]

106. Tan Z, Randall G, Fan J, et al. Allele-specific targeting of microRNAs to HLA-G and risk of asthma. American journal of human genetics. 2007 Oct; 81(4):829–834. [PubMed: 17847008]

107. Jardim MJ, Dailey L, Silbajoris R, Diaz-Sanchez D. Distinct microRNA expression in human airway cells of asthmatic donors identifies a novel asthma-associated gene. American journal of respiratory cell and molecular biology. 2012 Oct; 47(4):536–542. [PubMed: 22679274]
108. Solberg OD, Ostrin EJ, Love MI, et al. Airway epithelial miRNA expression is altered in asthma. American journal of respiratory and critical care medicine. 2012 Nov 15; 186(10):965–974. [PubMed: 22955319]
109. Plank M, Maltby S, Mattes J, Foster PS. Targeting translational control as a novel way to treat inflammatory disease: the emerging role of microRNAs. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2013 Sep; 43(9):981–999. [PubMed: 23957346]
110. Huang JC, Babak T, Corson TW, et al. Using expression profiling data to identify human microRNA targets. Nature methods. 2007 Dec; 4(12):1045–1049. [PubMed: 18026111]
111. Sales G, Coppe A, Bisognin A, Biasiolo M, Bortoluzzi S, Romualdi C. MAGIA, a web-based tool for miRNA and Genes Integrated Analysis. Nucleic acids research. 2010 Jul.38:W352–W359. Web Server issue. [PubMed: 20484379]
112. Elkan-Miller T, Ulitsky I, Hertzano R, et al. Integration of transcriptomics, proteomics, and microRNA analyses reveals novel microRNA regulation of targets in the mammalian inner ear. PloS one. 2011; 6(4):e18195. [PubMed: 21483685]
113. Beck D, Ayers S, Wen J, et al. Integrative analysis of next generation sequencing for small non-coding RNAs and transcriptional regulation in Myelodysplastic Syndromes. BMC medical genomics. 2011; 4:19. [PubMed: 21342535]
114. Muniategui A, Pey J, Planes FJ, Rubio A. Joint analysis of miRNA and mRNA expression data. Briefings in bioinformatics. 2013 May; 14(3):263–278. [PubMed: 22692086]
115. Jalali S, Bhartiya D, Lalwani MK, Sivasubbu S, Scaria V. Systematic transcriptome wide analysis of lncRNA-miRNA interactions. PloS one. 2013; 8(2):e53823. [PubMed: 23405074]
116. Hu R, Pan W, Fedulov AV, et al. MicroRNA-10a controls airway smooth muscle cell proliferation via direct targeting of the PI3 kinase pathway. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2014 May; 28(5):2347–2357. [PubMed: 24522205]
117. Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. New England Journal of Medicine. 1981; 305(26):1551–1559. [PubMed: 6796882]
118. Nystad W, Roysamb E, Magnus P, Tambs K, Harris JR. A comparison of genetic and environmental variance structures for asthma, hay fever and eczema with symptoms of the same diseases: a study of Norwegian twins. Int J Epidemiol. 2005 Dec; 34(6):1302–1309. [PubMed: 15831566]
119. Norman RE, Carpenter DO, Scott J, Brune MN, Sly PD. Environmental exposures: an underrecognized contribution to noncommunicable diseases. Reviews on environmental health. 2013; 28(1):59–65. [PubMed: 23612529]
120. Baldini M, Lohman IC, Halonen M, Erickson RP, Holt PG, Martinez FD. A Polymorphism* in the 5' flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum immunoglobulin E. American Journal of Respiratory and Cellular Molecular Biology. 1999 May; 20(5):976–983.
121. Ober C, Tselenko A, Cox NJ. Searching for asthma and atopy genes in the Hutterites: Genome-wide studies using linkage and association. American Journal of Respiratory and Critical Care Medicine. 2000 Mar.161(3):A600.
122. Zambelli-Weiner A, Ehrlich A, Stockton ML, et al. Evaluation of the CD14/−260 polymorphism and house dust endotoxin exposure in the Barbados asthma genetics study. Journal of Allergy and Clinical Immunology. 2005 in press.
123. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy. 2005 Dec; 35(12):1550–1556. [PubMed: 16393320]
124. Li YF, Gilliland FD, Berhane K, et al. Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. Am J Respir Crit Care Med. 2000 Dec; 162(6):2097–2104. [PubMed: 11112121]

125. Moshammer H, Hoek G, Luttmann-Gibson H, et al. Parental smoking and lung function in children: an international study. Am J Respir Crit Care Med. 2006 Jun 1; 173(11):1255–1263. [PubMed: 16484675]

126. Raherison C, Penard-Morand C, Moreau D, et al. In utero and childhood exposure to parental tobacco smoke, and allergies in schoolchildren. Respir Med. 2007 Jan; 101(1):107–117. [PubMed: 16735111]

127. Colilla S, Nicolae D, Pluzhnikov A, et al. Evidence for gene-environment interactions in a linkage study of asthma and smoking exposure. Journal of Allergy and Clinical Immunology. 2003; 111(4):840–846. [PubMed: 12704367]

128. Choudhry S, Avila PC, Nazario S, et al. CD14 tobacco gene-environment interaction modifies asthma severity and immunoglobulin E levels in Latinos with asthma. Am J Respir Crit Care Med. 2005 Jul 15; 172(2):173–182. [PubMed: 15879416]

129. Meyers DA, Postma DS, Stine OC, et al. Genome screen for asthma and bronchial hyperresponsiveness: interactions with passive smoke exposure. J Allergy Clin Immunol. 2005 Jun; 115(6):1169–1175. [PubMed: 15940130]

130. Lovinsky-Desir S, Miller RL. Epigenetics, asthma, and allergic diseases: a review of the latest advancements. Current allergy and asthma reports. 2012 Jun; 12(3):211–220. [PubMed: 22451193]

131. Brand S, Kesper DA, Teich R, et al. DNA methylation of TH1/TH2 cytokine genes affects sensitization and progress of experimental asthma. The Journal of allergy and clinical immunology. 2012 Jun; 129(6):1602–1610. e1606. [PubMed: 22277202]

132. Mikhaylova L, Zhang Y, Kobzik L, Fedulov AV. Link between epigenomic alterations and genome-wide aberrant transcriptional response to allergen in dendritic cells conveying maternal asthma risk. PloS one. 2013; 8(8):e70387. [PubMed: 23950928]

133. Gaffin JM, Raby BA, Petty CR, et al. beta-2 adrenergic receptor gene methylation is associated with decreased asthma severity in inner-city schoolchildren: asthma and rhinitis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2014 May; 44(5):681–689. [PubMed: 24131275]

134. Collison A, Siegle JS, Hansbro NG, et al. Epigenetic changes associated with disease progression in a mouse model of childhood allergic asthma. Disease models & mechanisms. 2013 Jul; 6(4): 993–1000. [PubMed: 23611895]

135. Durham A, Chou PC, Kirkham P, Adcock IM. Epigenetics in asthma and other inflammatory lung diseases. Epigenomics. 2010 Aug; 2(4):523–537. [PubMed: 22121972]

136. Sanders YY, Ambalavanan N, Halloran B, et al. Altered DNA methylation profile in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine. 2012 Sep 15; 186(6):525–535. [PubMed: 22700861]

137. Pandit KV, Milosevic J, Kaminski N. MicroRNAs in idiopathic pulmonary fibrosis. Translational research : the journal of laboratory and clinical medicine. 2011 Apr; 157(4):191–199. [PubMed: 21420029]

138. Dakhlallah D, Batte K, Wang Y, et al. Epigenetic regulation of miR-17∼92 contributes to the pathogenesis of pulmonary fibrosis. American journal of respiratory and critical care medicine. 2013 Feb 15; 187(4):397–405. [PubMed: 23306545]

139. Huang SK, Scruggs AM, Donaghy J, et al. Histone modifications are responsible for decreased Fas expression and apoptosis resistance in fibrotic lung fibroblasts. Cell death & disease. 2013; 4:e621. [PubMed: 23640463]

140. Cheng RY, Shang Y, Limjunyawong N, et al. Alterations of the lung methylome in allergic airway hyper-responsiveness. Environmental and molecular mutagenesis. 2014 Apr; 55(3):244–255. [PubMed: 24446183]

141. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. Bmj. 1993 Apr 17; 306(6884):1034–1037. [PubMed: 8098238]

142. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, Group SS. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006 Jan; 129(1):15–26. [PubMed: 16424409]

143. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Annals of internal medicine. 2006 Jun 20; 144(12):904–912. [PubMed: 16754916]

144. Adel-Patient K, Creminon C, Bernard H, et al. Evaluation of a high IgE-responder mouse model of allergy to bovine beta-lactoglobulin (BLG): development of sandwich immunoassays for total and allergen-specific IgE, IgG1 and IgG2a in BLG-sensitized mice. Journal of Immunological Methods. 2000 Feb 21; 235(1–2):21–32. [PubMed: 10675754]

145. Chan MT, Leung DY, Szefler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. The Journal of allergy and clinical immunology. 1998 May; 101(5): 594–601. [PubMed: 9600494]

146. Serra-Batlles J, Plaza V, Morejon E, Comella A, Brugues J. Costs of asthma according to the degree of severity. The European respiratory journal. 1998 Dec; 12(6):1322–1326. [PubMed: 9877485]

147. Miller SM, Ortega VE. Pharmacogenetics and the development of personalized approaches for combination therapy in asthma. Current allergy and asthma reports. 2013 Oct; 13(5):443–452. [PubMed: 23912588]

148. Poon AH, Tantisira KG, Litonjua AA, et al. Association of corticotropin-releasing hormone receptor-2 genetic variants with acute bronchodilator response in asthma. Pharmacogenetics and genomics. 2008 May; 18(5):373–382. [PubMed: 18408560]

149. Himes BE, Jiang X, Hu R, et al. Genome-wide association analysis in asthma subjects identifies SPATS2L as a novel bronchodilator response gene. PLoS genetics. 2012 Jul.8(7):e1002824. [PubMed: 22792082]

150. Tantisira KG, Small KM, Litonjua AA, Weiss ST, Liggett SB. Molecular properties and pharmacogenetics of a polymorphism of adenylyl cyclase type 9 in asthma: interaction between beta-agonist and corticosteroid pathways. Human molecular genetics. 2005 Jun 15; 14(12):1671–1677. [PubMed: 15879435]

151. Silverman EK, Kwiatkowski DJ, Sylvia JS, et al. Family-based association analysis of beta2-adrenergic receptor polymorphisms in the childhood asthma management program. The Journal of allergy and clinical immunology. 2003 Nov; 112(5):870–876. [PubMed: 14610472]

152. Martinez FD, Graves PE, Baldini M, Solomon S, Erickson R. Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. The Journal of clinical investigation. 1997 Dec 15; 100(12):3184–3188. [PubMed: 9399966]

153. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. Thorax. 2000 Sep; 55(9):762–767. [PubMed: 10950895]

154. Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. American journal of respiratory and critical care medicine. 2000 Jul; 162(1):75–80. [PubMed: 10903223]

155. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet. 2004 Oct 23–29; 364(9444):1505–1512. [PubMed: 15500895]

156. Wechsler ME, Lehman E, Lazarus SC, et al. beta-Adrenergic receptor polymorphisms and response to salmeterol. American journal of respiratory and critical care medicine. 2006 Mar 1; 173(5):519–526. [PubMed: 16322642]

157. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to longacting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. Lancet. 2007 Dec 22; 370(9605):2118–2125. [PubMed: 18156033]

158. Bleecker ER, Yancey SW, Baitinger LA, et al. Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. The Journal of allergy and clinical immunology. 2006 Oct; 118(4):809–816. [PubMed: 17030231]

159. Litonjua AA, Lasky-Su J, Schneiter K, et al. ARG1 is a novel bronchodilator response gene: screening and replication in four asthma cohorts. American journal of respiratory and critical care medicine. 2008 Oct 1; 178(7):688–694. [PubMed: 18617639]
160. Tantisira KG, Lake S, Silverman ES, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum Mol Genet. 2004 Jul 1; 13(13):1353–1359. [PubMed: 15128701]
161. Hawkins GA, Lazarus R, Smith RS, et al. The glucocorticoid receptor heterocomplex gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. The Journal of allergy and clinical immunology. 2009 Jun; 123(6):1376–1383. e1377. [PubMed: 19254810]
162. Tantisira KG, Hwang ES, Raby BA, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. Proceedings of the National Academy of Sciences of the United States of America. 2004 Dec 28; 101(52):18099–18104. [PubMed: 15604153]
163. Ye YM, Lee HY, Kim SH, et al. Pharmacogenetic study of the effects of NK2R G231E G>A and TBX21 H33Q C>G polymorphisms on asthma control with inhaled corticosteroid treatment. Journal of clinical pharmacy and therapeutics. 2009 Dec; 34(6):693–701. [PubMed: 20175803]
164. Kim SH, Ye YM, Lee HY, Sin HJ, Park HS. Combined pharmacogenetic effect of ADCY9 and ADRB2 gene polymorphisms on the bronchodilator response to inhaled combination therapy. Journal of clinical pharmacy and therapeutics. 2011 Jun; 36(3):399–405. [PubMed: 21545619]
165. Berce V, Kozmus CE, Potocnik U. Association among ORMDL3 gene expression, 17q21 polymorphism and response to treatment with inhaled corticosteroids in children with asthma. The pharmacogenomics journal. 2013 Dec; 13(6):523–529. [PubMed: 22986918]
166. Wooten EC, Huggins GS. Mind the dbGAP: the application of data mining to identify biological mechanisms. Mol Interv. 2011 Apr; 11(2):95–102. [PubMed: 21540468]
167. O'Driscoll A, Daugelaite J, Sleator RD. 'Big data', Hadoop and cloud computing in genomics. J Biomed Inform. 2013 Oct; 46(5):774–781. [PubMed: 23872175]
168. Barnes KC. Genomewide association studies in allergy and the influence of ethnicity. Curr Opin Allergy Clin Immunol. 2010 Oct; 10(5):427–433. [PubMed: 20724922]
169. Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. The New England journal of medicine. 2010 Mar 18; 362(11):975–985. [PubMed: 20197425]
170. Wechsler ME, Castro M, Lehman E, et al. Impact of race on asthma treatment failures in the asthma clinical research network. American journal of respiratory and critical care medicine. 2011 Dec 1; 184(11):1247–1253. [PubMed: 21885625]

Appendix A

A summary of genome-wide association studies (GWAS) performed on allergic diseases (*p*-values on the discovery sample $p<10\text{-}^{5}$).

Population	Location	Reported gene	Adjacent gene (L,R)	References
Asthma				
European	1p13.1	*IGSF3*	*CD58, MIR320B1*	Ding et al 2013 [1]
European	1q25.3	*XPR1*	*ACBD6, KIAA1614*	Ding et al 2013[1]
European	1q44	*C1orf100*	*CEP170, HNRNPU*	Forno et al 2012[2]
European	1q21.3	*IL6R*	*SHE, LOC101928101*	Ferreira et al 2011[3]
Mixed Ethnicities	1q23.1	*PYHIN1*	*IFI16, LOC646377*	Torgerson et al 2011[4]
Mixed Ethnicities	1q21.3	*CRCT1*	*LCE5A, LCE3E*	Torgerson et al 2011[4]
European	1q31.3	*DENND1B*	*CRB1, C10rf53*	Sleiman et al 2010[5]

Population	Location	Reported gene	Adjacent gene (L,R)	References
Korean	2p22.2	*CRIM1*	*LOC10028911, FEZ2*	Kim et al 2013[6]
Korean	2q36.2	*DOCK10*	*CUL3, MIR4439*	Kim et al 2013[6]
European	2p22.1	*Intergenic*	*THUMPD2, SLC8A1-AS1*	Ding et al 2013[1]
European	2q34	*CPS1*	*LOC102724820, ERBB4*	Melen et al 2013[7]
European	2p23.3	*ADCY3*	*NCOA1, DNAJC27-AS1*	Melen et al 2013[7]
European	2p23.3	*ADCY3*	*PTRHD1, DNAJC27*	Melen et al 2013[7]
European	2p23.3	*EFR3B*	*DNAJC27, DNMT3A*	Melen et al 2013[7]
European	2p23.3	*Intergenic*	*ADCY3, DNAJC27*	Melen et al 2013[7]
European	2q12.1	*IL1RL1*	*IL1R1, IL18RAP*	Ramasamy et al 2012[8]
European	2q33.1	*SPATS2L*	*TYW5, SGOL2*	Himes et al 2012[9]
European	2q12.1	*IL1RL1, IL18R1*	*IL1R2, IL18RAP*	Wan et al 2012[10]
Mixed Ethnicities	2q12.1	*IL1RL1*	*IL1R1, IL18RAP*	Torgerson et al 2011[4]
European	2q12.1	*IL18R1*	*IL1RL1, IL18RAP*	Moffatt et al 2010[11]
European	3q13.2	*ATG3*	*BTLA, SLC3A5*	Ding et al 2013[1]
European	3p22.3	*Intergenic*	*LOC101928135, ARPP21*	Ding et al 2013[1]
European	3q26.32	*Intergenic*	*LOC102724550, KCNB2*	Ding et al 2013[1]
European	3q12.2	*ABI3BP*	*TFG, IMPG2*	Ding et al 2013[1]
European	3p26.2	*IL5RA*	*CNTN4, LRRN1*	Forno et al 2012[2]
Korean	4q26	*SYNPO2*	*SEC24D, MYOZ2*	Kim JH et al 2013[6]
European	4q12	*Intergenic*	*IGFBP7, LPHN3*	Ding et al 2013[1]
European	4p14	*KLHL5*	*TMEM156, WDR19*	Ding et al 2013[1]
European	4p15.1	*Intergenic*	*PCDH7, ARAP2*	Melen et al 2013[7]
Japanese	4q31.21	*LOC729675*	*INPP4B, USP38*	Hirota et al 2011[12]
Japanese	4q31.21	*GAB1*	*USP38, SMARCA5*	Hirota et al 2011[12]
European	5q31.1	*C5orf56*	*SLC22A5, IRF1*	Wan et al 2012[10]
European	5q31.3	*NDFIP1*	*GNPDA1, NDFIP1*	Wan et al 2012[10]
Japanese	5q22.1	*TSLP*	*SLC25A46, WDR36*	Hirota et al 2011[12]
Mixed Ethnicities	5q22.1	*TSLP*	*SLC25A46, WDR36*	Torgerson et al 2011[4]
European	5q31.1	*SLC22A5*	*LOC553103, C5orf56*	Moffatt et al 2010[11]
European	5q31.1	*IL13*	*RAD50, IL4*	Moffatt et al 2010[11]
European	5q31.1	*RAD50*	*IL5, IL13*	Li et al 2010[13]
European	5q12.1	*PDE4D*	*RAB3C, PART1*	Himes et al 2009[14]
European	6p21.1	*Intergenic*	*CDC5L, SUPT3H*	Ding et al 2013[1]
European	6q21	*Intergenic*	*RFPL4B, LINC01268*	Ding et al 2013[1]
European	6p12.3	*AL139097.1*	*TFA2B, PKHD1*	Melen et al 2013[7]
European	6p21.32	*HLA-DQA1*	*HLA-DRB1, HLA-DQB1*	Lasky-Su et al 2012[15]
Korean	6p21.32	*HLA-DPB1*	*HLA-DPA1, HLA-DPB2*	Park et al 2013[16]
European	6p21.32	*BTNL2*	*HCG23, HLA-DRA*	Ramasamy et al 2012[8]

Population	Location	Reported gene	Adjacent gene (L,R)	References
European	6q27	*T*	*LINC00602, PRR18*	Tantisira et al 2012[17]
Japanese	6p21.32	*PBX2*	*AGER, GPSM3*	Hirota et al 2011[12]
Japanese	6p21.32	*NOTCH4*	*GPSM2, C6orf10*	Hirota et al 2011[12]
Japanese	6p21.32	*C6orf10*	*NOTCH4, HCG23*	Hirota et al 2011[12]
Japanese	6p21.32	*BTNL2*	*HCG23, HLA-DRA*	Hirota et al 2011[12]
Japanese	6p21.32	*HLA-DRA*	*BTNL2, HLA-DRB5*	Hirota et al 2011[12]
Japanese	6p21.32	*HLA-DQB1*	*HLA-DQA1, HLA-DQA2*	Hirota et al 2011[12]
Japanese	6p21.32	*HLA-DQA2*	*HLA-DQB1, HLA-DQB2*	Hirota et al 2011[12]
Japanese	6p21.32	*HLA-DOA*	*BRD2, HLA-DPA1*	Hirota et al 2011[12]
Japanese	6p21.32	*HLA-DPB1*	*HLA-DPA1, HLA-DPB2*	Noguchi et al 2011[18]
European	6p21.32	*HLA-DQB1*	*HLA-DQA1, HLA-DQA2*	Moffatt et al 2010[11]
European	7p15.3	*Intergenic*	*NPY, STK31*	Ding et al 2013[1]
European	7q32.3	*MKLN1*	*LINC-PINT, PODXL*	Ding et al 2013[1]
Korean	8q11.23	*OPRK1*	*NPBWR1, ATP6V1H*	Kim et al 2013[6]
European	8p12	*Intergenic*	*DUSP26, UNC5D*	Ding et al 2013[1]
European	8q24.23	*COL22A1*	*FAM135B, KCNK9*	Duan et al 2014[19]
Japanese	8q24.11	*SLC30A8*	*AARD, MED30*	Noguchi et al 2011[18]
Korean	9p13.3	*TLN1*	*TPM2, MIR6852*	Kim JH et al 2013[6]
European	9p23	*Intergenic*	*PTPRD-AS2, TYRP1*	Ding et al 2013[1]
European	9q21.33	*Intergenic*	*ZCCHC6, GAS1*	Ding et al 2013[1]
European	9p22.1	*SLC24A2*	*ACER2, MLLT3*	Melen et al 2013[7]
European	9q33.3	*DENND1A*	*CRB2, LHX2*	Melen et al 2013[7]
European	9p21.1	*ACO1*	*LINX01242, DDX58*	Wan et al 2012[10]
Mixed Ethnicities	9p24.1	*IL33*	*RANBP6, TPD52L3*	Torgerson et al 2011[4]
European	9p24.1	*IL33*	*RANBP6, TPD52L3*	Moffatt et al 2010[11]
Mexican	9q21.31	*TLE4, CHCHD9*	*LOC101927450, LOC101927477*	Hancock et al 2009[20]
Korean	9p21.3	*Intergenic*	*SLC24A2, MLLT3*	Kim SH et al 2009[21]
European	10q24.2	*HPSE2*	*HPS1, CNNM1*	Ding et al 2013[1]
European	10q22.1	*PSAP*	*CDH23, CHST3*	Ding et al 2013[1]
European	10p15.1	*PRKCQ*	*LOC399715, PRKCQ-AS1*	Melen et al 2013[7]
European	10q26.11	*EMX2*	*PDZD8, RAB11FIP2*	Li et al 2013[22]
European	10p15.1	*PRKCQ*	*LOC101927964, LINC00702*	Duan et al 2014[19]
European	10q21.1	*PRKG1*	*A1CF, PRKG1-AS1*	Ferreira et al 2011[3]
Japanese	10p14	*LOC338591*	*LINC00708, LOC101928272*	Hirota et al 2011[12]
Korean	10q21.3	*CTNNA3*	*LOC101928913,*	Kim SH et al 2009[21]
Korean	11q24.1	*OR6X1*	*ZNF202, OR6M1*	Kim JH et al 2013[6]
European	11q13.4	*P2RY2*	*FCHSD2, P2RY2*	Melen et al 2013[7]

Population	Location	Reported gene	Adjacent gene (L,R)	References
European	11q24.2	*NR*	*LOC101929497, ETS1*	Forno et al 2012[2]
European	11q13.5	*LRRC32*	*C11orf30, GUCY2EP*	Ferreira et al 2011[3]
Mixed ethnicities	11q23.2	*C11orf71*	*LOC101928940, RBM7*	Torgerson et al 2011[4]
Japanese	12q13.2	*CDK2*	*PMEL, RAB5B*	Hirota et al 2011[12]
Japanese	12q13.2	*IKZF4*	*SUOX, RPS26*	Hirota et al 2011[12]
European	13q13.1	*STARD13, RP11-81F11.3*	*KL, RFC3*	Melen et al 2013[7]
European	13q13.3	*NR*	*MIR548F5, DCLK1*	Forno et al 2012[2]
European	13q21.31	*PCDH20*	*MIR3169, LINC00358*	Ferreira et al 2011[3]
Korean	13q12.13	*Intergenic*	*GPR12, USP12*	Kim SH et al 2009[21]
Korean	14q32.2	*LOC730217*	*C14orf64, C14orf177*	Kim JH et al 2013[6]
European	15q22.33	*SMAD3*	*SMAD6, AAGAB*	Moffatt et al 2010[11]
European	15q22.2	*RORA*	*LOC101928784, VPS13C*	Moffatt et al 2010[11]
European	15q21.2	*SCG3*	*DMXL2, LYSMD2*	Li et al 2010[13]
Korean	16q23.3	*CDH13*	*MPH0SPH6, MLYCD*	Kim JH et al 2013[6]
European	17q21.32	*Intergenic*	*MIR196A1, PRAC1*	Melen et al 2013[7]
European	17q21.32	*Intergenic*	*MIR196A1, PRAC1*	Melen et al 2013[7]
European	17q12	*ORMDL3*	*GSDMB, LRRC3C*	Wan et al 2012[10]
European	17p12	*NR*	*HS3ST3A1, COX10-AS1*	Forno et al 2012[2]
Mixed ethnicities	17q12	*GSDMB*	*ZPBP2, ORMDL3*	Torgerson et al 2011[4]
European	17q12	*ORMDL3*	*GSDMB, LRRC3C*	Ferreira et al 2011[23]
European	17q12	*GSDMB*	*ZPBP2, ORMDL3*	Moffatt et al 2010[11]
European	17q21.1	*GSDMA*	*LRRC3C, PSMD3*	Moffatt et al 2010[11]
European	17q12	*ORMDL3*	*GSDMB, LRRC3C*	Moffatt et al 2010[11]
European	18p11.31	*LPIN2*	*EMILIN2, MYOM1*	Melen et al 2013[7]
European	18p11.32	*YES1*	*ENOSF1, ADCYAP1*	Li et al 2013[22]
Korean	19q13.43	*ZNF71*	*ZNF470, SMIM17*	Kim JH et al 2013[6]
European	19p13.11	*IL12RB1*	*AARDC2, MAST3*	Li et al 2013[22]
European	19q13.42	*ZNF665*	*ZNF347, ZNF818P*	Wan et al 2012[10]
European	20p12.3	Intergenic	*MIR8062, HA01*	Ding et al 2013[1]
European	20q13.2	Intergenic	*LOC101927700, TSHZ2*	Melen et al 2013[7]
European	20p13	*KIAA1271*	*AP5S1, MAVS*	Li et al 2010[13]
European	22q13.31	*UPK3A*	*NUP50, FAM118A*	Li et al 2013[22]
European	22q12.3	*IL2RB*	*TMPRSS6, C1QTNF6*	Moffatt et al 2010[11]
European	NR	Intergenic		Wan et al 2012[10]
Atopic Dermatitis				
European	1q21.3	*FLG*	*HRNR, FLG2*	Weidinger et al 2013[24]
Chinese	1q21.3	*FLG*	*HRNR, FLG2*	Sun et al 2011[25]
Japanese	2q12.1	*IL1RL1, IL18R1, IL18RAP*	*IL1R1, IL18RAP, IL1R2*	Hirota et al 2012[26]
Japanese	2q13	*LOC100505634*	*BCL2L11, MIR4435-1*	Hirota et al 2012[26]

Population	Location	Reported gene	Adjacent gene (L,R)	References
Japanese	3p22.3	*GLB1*	*CCR4, SUSD5*	Hirota et al 2012[26]
Japanese	3q13.2	*CCDC80*	*LINC01279, LOC101929694*	Hirota et al 2012[26]
European	5q31.1	*IL13*	*RAD50, IL4*	Weidinger et al 2013[24]
Japanese	5q31.1	*IL13*	*RAD50, IL4*	Hirota et al 2012[26]
European	5q31.1	*IL13*	*RAD50, IL4*	Paternoster et al 2012[27]
European	6p21.33	*TNXB*	*CYP21A2, ATF6B*	Weidinger et al 2013[24]
Japanese	6p21.33	*HLA-C*	*HCG27, HLA-B*	Hirota et al 2012[26]
Japanese	6p21.32	*GPSM3*	*PBX2, NOTCH4*	Hirota et al 2012[26]
Japanese	6p21.32	*C6orf10*	*NOTCH4, HCG23*	Hirota et al 2012[26]
European	6p21.33	*BAT1*	*MCCD1, DDX39B*	Paternoster et al 2012[27]
Japanese	7p22.2	*CARD11*	*GNA12, SDK1*	Hirota et al 2012[26]
Japanese	8q24.21	*MIR1208*	*PVT1, LINC00977*	Hirota et al 2012[26]
European	8q21.13	*ZBTB10*	*MIR5708, ZNF704*	Paternoster et al 2012[27]
Japanese	10q21.2	*ZNF365*	*LOC283045, EGR2*	Hirota et al 2012[26]
Japanese	10q21.3	*ADO, EGR2*	*ZNF365, NRBF2*	Hirota et al 2012[26]
European	11q13.5	*C11orf30*	*LOC100506127, LRRC32*	Weidinger et al 2013[24]
Japanese	11p15.4	*OR10A3, NLRP10*	*OR10A3, NLRP10*	Hirota et al 2012[26]
Japanese	11q13.5	*C11orf30*	*LOC100506127, LRRC32*	Hirota et al 2012[26]
Japanese	11q13.1	*OVOL1*	*AP5B1, SNX32*	Hirota et al 2012[26]
European	11q13.1	*OVOL1*	*AP5B1, SNX32*	Paternoster et al 2012[27]
European	11q13.5	*C11orf30*	*LOC100506127, LRRC32*	2009[28]
Japanese	16p13.13	*CLEC16A*	*DEXI, SOCS1*	Hirota et al 2012[26]
European	19p13.2	*ACTL9*	*ADAMTS10, OR2Z1*	Paternoster et al 2012[27]
Japanese	20q13.2	*CYP24A1, PFDN4*	*CYP24A1, PFDN4*	Hirota et al 2012[26]
European	22q12.3	*NCF4*	*PVALB, CSF2RB*	Paternoster et al 2012[27]
Atopy				
European	2p21	*SGK493*	*C2orf91, PKDCC*	Castro-Giner et al 2009[29]
Allergic Rhinitis				
European	1p36.13	*CROCC*	*MIR3675, MFAP2*	Ramasamy et al 2011[30]
European	5q22.1	*TMEM232, SLCA25A46*	*LOC100289673, TSLP*	Ramasamy et al 2011[30]
European	5q22.1 5q23.1	*TSLP*	*SLC25A46, WDR36 LOC101927190,*	Ramasamy et al 2011[30]
European		*SEMA6A*	*LOC102467223*	Ramasamy et al 2011[30]

Population	Location	Reported gene	Adjacent gene (L,R)	References
European	7p14.1	*GLI3*	*INHBA-AS1, LINC01448*	Ramasamy et al 2011[30]
European	11q13.5	*C11orf30, LRRC32*	*LOC100506127, GUCY2EP*	Ramasamy et al 2011[30]
European	14q23.1	*PPM1A, DHRS7*	*PCNXL4, C14orf39*	Ramasamy et al 2011[30]
European	16p13.13	*CLEC16A*	*DEXI, SOCS1*	Ramasamy et al 2011[30]
European	20p11.21	*ENTPD6*	*LOC101926889, PYGB*	Ramasamy et al 2011[30]
Total & Specific IgE				
European	1p32.3	*EPS15*	*TTC39A, OSBPL9*	Ramasamy et al 2011[30]
European	1q23.2	*DARC*	*CADM3-AS1, ACKR1*	Granada et al 2012[31]
European	1q23.2	*FCER1A*	*ACKR1, OR10J3*	Weidinger et al 2008[32]
European	1q23.2	*FCER1A*	*Mus Olfr418-ps1,*	Granada et al 2012[31]
European	1q23.2	*OR10J3*	*FCER1A, OR10J1*	Granada et al 2012[31]
European	1q25.2	*ABL2*	*TOR3A, SOAT1*	Ramasamy et al 2011[30]
Korean	2p22.2	*CRIM1*	*LOC100288911, FEZ2*	Kim et al 2013[6]
European	2p25.1	*ID2*	*LOC100506299, MBOAT2*	Granada et al 2012[31]
Korean	2q36.2	*DOCK10*	*CUL3, NYAP2*	Kim et al 2013[6]
Mixed ethnicities	3p14.1	*SUCLG2*	*MIR4272, SUCLG2-AS1*	Levin et al 2013[33]
European	3q22.1	*TMEM108*	*NPHP3-AS1, BFSP2*	Ramasamy et al 2011[30]
European	3q28	*LPP*	*BCL6, TPRG1-AS1*	Granada et al 2012[31]
Korean	4q26	*SYNPO2*	*SEC240, MYOZ2*	Kim et al 2013[6]
European	4q27	*IL2*	*ADAD1, IL21*	Ramasamy et al 2011[30]
European	5p15.2	*DNAH5 TMEM232,*	*LINC01194, TRIO*	Ramasamy et al 2011[30]
European	5q22.1	*SLCA25A46*	*LOC100289673, TSLP*	Ramasamy et al 2011[30]
European	5q31.1	*IL13*	*BC042122, IL4*	Granada et al 2012[31]
European	5q31.1	*RAD50*	*IL5, IL13*	Weidinger et al 2008[32]
European	6p21.32	*HLA region*	*HLA-DQB1, HLADQA2*	Ramasamy et al 2011[30]
European	6p21.32	*HLA-DQA2*	*HLA-DQB1, HLA-DQB2*	G ranada et al 2012[31]
Mixed ethnicities	6p21.32	*HLA-DQA2*	*HLA-DQB1, HLA-DQB2*	Levin et al 2013[33]

Population	Location	Reported gene	Adjacent gene (L,R)	References
Mixed ethnicities	6p21.32	*HLA-DQB1*	*HLA-DQA1, HLADQA2*	Levin et al 2013[33]
European	6p22.1	*HLA-G*	*LOC554223, HLA-H*	Granada et al 2012[31]
European	6p22.1	*HLA-A*	*HCG4B, HCG9*	Granada et al 2012[31]
Korean	8q11.23	*OPRK1*	*NPBWR1, ATP6V1H*	Kim et al 2013[6]
Korean	9p13.3	*TLN1*	*TPM2, CREB3*	Kim et al 2013[6]
Korean	11q24.1	*OR6X1*	*ZNF202, ORM1*	Kim et al 2013[6]
European	12q13.3	*STAT6, NAB2*	*TMEM194A, LRP1*	Granada et al 2012[31]
Korean	14q32.2	*LOC730217*	*C14orf64, C14orf177*	Kim et al 2013[6]
European	16p12.1	*IL4R*	*FLJ21408, IL21R*	Granada et al 2012[31]
European	16p13.2	*Intergenic*	*MIR548X, MIR7641-2*	Ramasamy et al 2011[30]
Mixed ethnicities	16q22.1	*WWP2*	*NOB1, PDXDC2P*	Levin et al 2013[33]
Korean	16q23.3	*CDH13*	*MPHOSPH 6, LOC102724163*	Kim et al 2013[6]
Korean	19q13.43	*ZNF71*	*ZNF470, SMIM17*	Kim et al 2013[6]
Airway hyperresponsiveness				
European	2q36.3	*AGFG1*	*TM4SF20, C2orf83*	Himes et al 2013[34]

Mixed ethnicities = African American/African Caribbean, Latino, European ancestry

References for Table 1

1. Ding L, et al. Rank-based genome-wide analysis reveals the association of ryanodine receptor-2 gene variants with childhood asthma among human populations. Hum Genomics. 2013; 7:16. [PubMed: 23829686]
2. Forno E, et al. Genome-wide association study of the age of onset of childhood asthma. J Allergy Clin Immunol. 2012; 130:83–90. e4. [PubMed: 22560479]
3. Ferreira MA, et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. Lancet. 2011; 378:1006–1014. [PubMed: 21907864]
4. Torgerson DG, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet. 2011; 43:887–892. [PubMed: 21804549]
5. Sleiman PM, et al. Variants of DENND1B associated with asthma in children. N Engl J Med. 2010; 362:36–44. [PubMed: 20032318]
6. Kim JH, et al. A genome-wide association study of total serum and mite-specific IgEs in asthma patients. PLoS One. 2013; 8:e71958. [PubMed: 23967269]
7. Melen E, et al. Genome-wide association study of body mass index in 23 000 individuals with and without asthma. Clin Exp Allergy. 2013; 43:463–474. [PubMed: 23517042]
8. Ramasamy A, et al. Genome-wide association studies of asthma in population-based cohorts confirm known and suggested loci and identify an additional association near HLA. PLoS One. 2012; 7:e44008. [PubMed: 23028483]
9. Himes BE, et al. Genome-wide association analysis in asthma subjects identifies SPATS2L as a novel bronchodilator response gene. PLoS Genet. 2012; 8:e1002824. [PubMed: 22792082]
10. Wan YI, et al. Genome-wide association study to identify genetic determinants of severe asthma. Thorax. 2012; 67:762–768. [PubMed: 22561531]
11. Moffatt MF, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010; 363:1211–1221. [PubMed: 20860503]

12. Hirota T, et al. Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population. Nat Genet. 2011; 43:893–896. [PubMed: 21804548]
13. Li X, et al. Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions. J Allergy Clin Immunol. 2010; 125:328–335. e11. [PubMed: 20159242]
14. Himes BE, et al. Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. Am J Hum Genet. 2009; 84:581–593. [PubMed: 19426955]
15. Lasky-Su J, et al. HLA-DQ strikes again: genome-wide association study further confirms HLA-DQ in the diagnosis of asthma among adults. Clin Exp Allergy. 2012; 42:1724–1733. [PubMed: 23181788]
16. Park BL, et al. Genome-wide association study of aspirin-exacerbated respiratory disease in a Korean population. Hum Genet. 2013; 132:313–321. [PubMed: 23180272]
17. Tantisira KG, et al. Genome-wide association identifies the T gene as a novel asthma pharmacogenetic locus. Am J Respir Crit Care Med. 2012; 185:1286–1291. [PubMed: 22538805]
18. Noguchi E, et al. Genome-wide association study identifies HLA-DP as a susceptibility gene for pediatric asthma in Asian populations. PLoS Genet. 2011; 7:e1002170. [PubMed: 21814517]
19. Duan QL, et al. A genome-wide association study of bronchodilator response in asthmatics. Pharmacogenomics J. 2014; 14:41–47. [PubMed: 23508266]
20. Hancock DB, et al. Genome-wide association study implicates chromosome 9q21.31 as a susceptibility locus for asthma in mexican children. PLoS Genet. 2009; 5:e1000623. [PubMed: 19714205]
21. Kim SH, et al. Alpha-T-catenin (CTNNA3) gene was identified as a risk variant for toluene diisocyanate-induced asthma by genome-wide association analysis. Clin Exp Allergy. 2009; 39:203–212. [PubMed: 19187332]
22. Li X, et al. Genome-wide association study identifies TH1 pathway genes associated with lung function in asthmatic patients. J Allergy Clin Immunol. 2013; 132:313–320. e15. [PubMed: 23541324]
23. Ferreira MA, et al. Association between ORMDL3, IL1RL1 and a deletion on chromosome 17q21 with asthma risk in Australia. Eur J Hum Genet. 2011; 19:458–464. [PubMed: 21150878]
24. Weidinger S, et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. Hum Mol Genet. 2013; 22:4841–4856. [PubMed: 23886662]
25. Sun LD, et al. Genome-wide association study identifies two new susceptibility loci for atopic dermatitis in the Chinese Han population. Nat Genet. 2011; 43:690–694. [PubMed: 21666691]
26. Hirota T, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. Nat Genet. 2012; 44:1222–1226. [PubMed: 23042114]
27. Paternoster L, et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. Nat Genet. 2012; 44:187–192. [PubMed: 22197932]
28. Esparza-Gordillo J, et al. A common variant on chromosome 11q13 is associated with atopic dermatitis. Nat Genet. 2009; 41:596–601. [PubMed: 19349984]
29. Castro-Giner F, et al. A pooling-based genome-wide analysis identifies new potential candidate genes for atopy in the European Community Respiratory Health Survey (ECRHS). BMC Med Genet. 2009; 10:128. [PubMed: 19961619]
30. Ramasamy A, et al. A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. J Allergy Clin Immunol. 2011; 128:996–1005. [PubMed: 22036096]
31. Granada M, et al. A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study. J Allergy Clin Immunol. 2012; 129:840–845. e21. [PubMed: 22075330]
32. Weidinger S, et al. Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus. PLoS Genet. 2008; 4:e1000166. [PubMed: 18846228]
33. Levin AM, et al. A meta-analysis of genome-wide association studies for serum total IgE in diverse study populations. J Allergy Clin Immunol. 2013; 131:1176–1184. [PubMed: 23146381]
34. Himes BE, et al. ITGB5 and AGFG1 variants are associated with severity of airway responsiveness. BMC Med Genet. 2013; 14:86. [PubMed: 23984888]

KEY POINTS

- Nearly 100 asthma genes/loci in addition to multiple genes/loci for AD, AR and IgE have been identified by genome-wide association studies (GWAS)
- Next generation sequencing (NGS) strategies are increasingly being used to hone in on the causal variants associated with allergic diseases
- A goal of the genetics of allergic disease is to better match individualized treatments to specific genotypes to improve therapeutic outcomes and minimize side effects

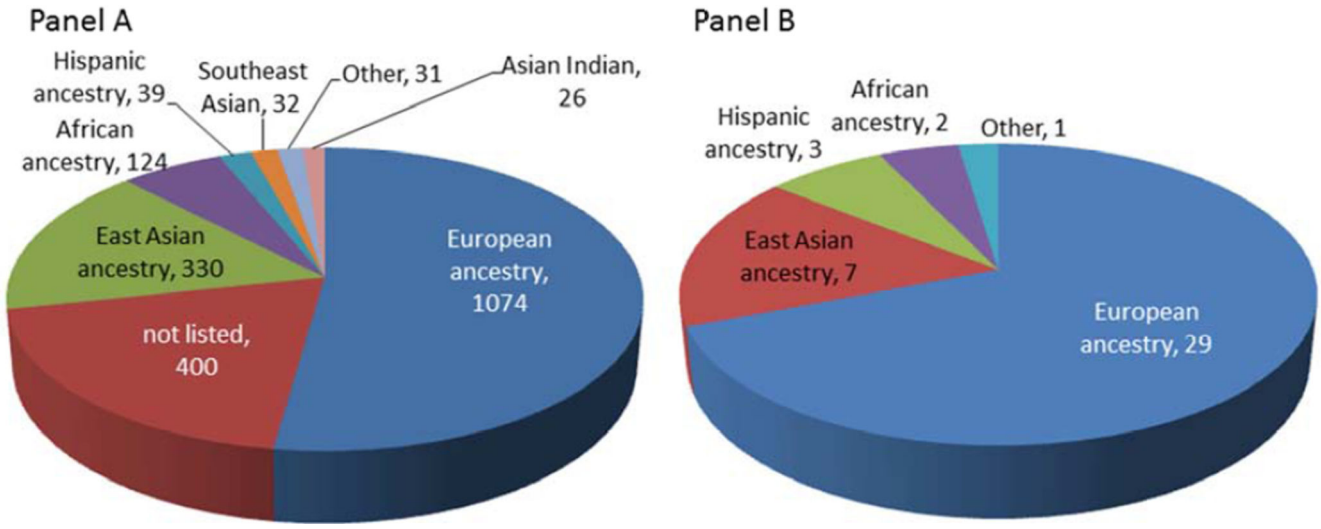

Figure 1.

Published genome-wide association studies (GWAS) to date according to ethnicity and race for all catalogued GWAS (**Panel A**) and asthma GWAS (**Panel B**). Data generated from the National Human Genome Research Institute's GWAS catalog website (http://www.genome.gov/gwastudies/).