

Genetics of Allergic Diseases



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KEYWORDS

- Allergic disease • Genetics • Single nucleotide polymorphism
- Genome-wide association study • Next-generation sequencing • Epigenetics
- Transcriptome

KEY POINTS

- Nearly 100 asthma genes/loci in addition to multiple genes/loci for atopic dermatitis, allergic rhinitis, and immunoglobulin E have been identified by genome-wide association studies.
- Next-generation sequencing 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 adverse effects.

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 increases in risk of developing asthma, AR, or AD with the presence of at least 1 parent with allergic disease, and greater than 3 times the risk if allergic disease occurred in more than 1 first-degree relative.⁷ To date, and despite the dramatic technological advances that have led to the identification of hundreds of genetic variants in genes associated

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with asthma, AD 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, 6 novel asthma genes were identified by positional cloning.^{18–23} Similarly, multiple linkage studies were performed for AD²⁴ and AR.^{25–29} It was frequently observed that loci overlapped across associated traits; for example, Daniels and colleagues⁸ 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. Alternatively, the multiethnic *Collaborative Study on the Genetics of Asthma* reported linkage peaks that were specific to different racial and 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 summarized elsewhere,^{32–35} representing the relative success of this approach.

THE GENOME-WIDE ASSOCIATION STUDIES ERA

Following completion of the Human Genome Project, the International HapMap Project^{36–38} cataloged genomes representing 4 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 analytical methods and investigating patterns of genetic variation. Simultaneously, the technological capacity to rapidly (and cheaply) genotype more than 1 million common (>5%) SNPs on thousands of DNA samples from patients phenotyped for various complex clinical traits took the spotlight, and the 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 more than 35 million sequenced variants cataloged in the TGP. In the span of only 7 years, over 1924 publications and 13,403 SNPs associated with various complex and quantitative traits^{42,43} have been generated by GWAS (Fig. 1A).

GWAS have been widely employed in the field of allergic disease. Although the precise number of GWAS are difficult to determine, approximately 40 asthma, 3 atopy,

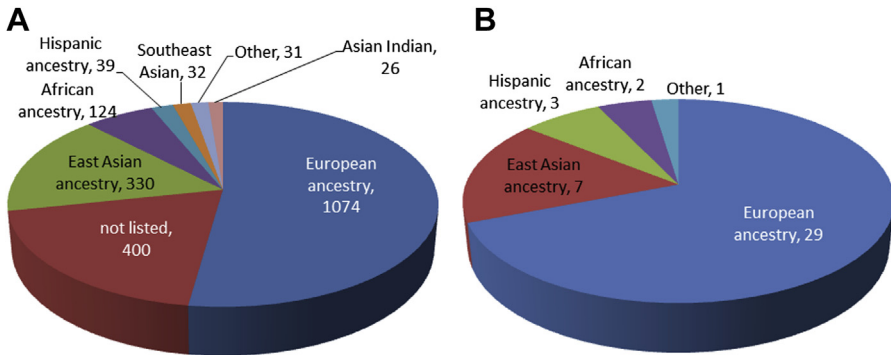


Fig. 1. Published GWAS to date according to ethnicity and race for all cataloged GWAS (A) and asthma GWAS (B). (Data from the National Human Genome Research Institute's GWAS catalog Web site. Accessed June 16, 2014. Available at: <http://www.genome.gov/gwastudies/>.)

and 3 AD GWAS (plus a study of >30,000 AD patients genotyped on the Immuno-chip⁴⁴) have been reported in the *Catalog of Published Genome-Wide Association Studies* (see Fig. 1B and summarized in Appendix A).^{42,43} A major outcome of GWAS in allergic disease has been the formation of national and international collaborations leading to consortia meta-analyses, which have 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 more than 26,000 cases and unaffected controls (eg, the European-based GABRIEL Consortium⁴⁶), five additional genes plus the 17q locus were strongly associated with asthma.⁴⁷ Following completion of 8 US-based, independent asthma GWAS, the National Heart Lung and Blood Institute (NHLBI)-supported EVE Consortium was established, comprising more than 12,000 European American, African American, and Hispanic cohorts plus more than 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 and colleagues, unpublished data, 2014).

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, 6 genes were strongly associated with asthma,⁴⁷ of which 3 genes (*IL33*, *ST2*, and the *IKZF3-ZBP2-GSDMB-ORMDL3* region on chromosome 17q21) were replicated in the EVE Consortium.⁴⁸ Independent GWAS have provided further support for these same loci.^{49–51} One of the strongest signals from the combined meta-analysis was for *IL1RL1*,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 ($P = 1.4 \times 10^{-8}$).

Lessons learned from candidate gene and positional cloning studies included the specificity of genetic associations to subphenotypes of allergic disease. For example, 2 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 (eg, the tendency for AD to precede asthma, food allergy, and AR) and the fact that approximately 70% of severe AD patients also have asthma and AR later in life can account for this overlap.⁵² Similar observations have come from GWAS of allergic diseases. For example, the associations with the *ORMDL3* locus have been strongest with childhood asthma,⁵³ and associations between SNPs in *IL1RL1* and *IL33* have been strongest for atopic asthma as opposed to nonatopic asthma.⁴⁹ From the GWAS performed total serum IgE levels, there has been relatively little overlap with genes contributing to risk of asthma (see [Appendix A](#)).

THE NEXT GENERATION OF ASTHMA GENETICS

Despite its success, discoveries from GWAS have contributed relatively little to the 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 less than 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,⁵⁴ which is likely a consequence of the array design (ie, 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 hypothesis⁵⁵ toward the role of rare variants (unlikely to be identified by GWAS⁵⁶) in non-Mendelian diseases,⁵⁷ particularly with the appreciation that rare variation constitutes the majority of polymorphisms across human populations.^{39,58}

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 sequencing⁵⁹ 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 2005⁶⁰ 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 toward gene discovery either by whole-exome (WES; ~30 Mb total) or whole-genome sequencing (WGS).⁶¹ Although 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 (ie, 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 with other types of changes.⁶¹

To date, there are limited examples of the application of next-generation sequencing (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 sequencing by oligonucleotide ligation and detection (SOLID) sequencing platform to accurately and simultaneously detect 161 of 170 mutations and deletions associated with primary immunodeficiency (PID) disorders.⁶² NGS has also been applied to the study of airway inflammation, including asthma. A study by Leung and colleagues⁶³ utilized the NGS 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. WES has been applied to a small family-based study⁶⁴ as well as asthmatics selected at both ends of a phenotype distribution (those with extreme severity phenotypes)⁶⁵ with limited success, and a large WGS (>1000 genomes) on asthma is underway.⁶⁶

MEASURING THE TRANSCRIPTOME IN ALLERGIC DISEASE AND ITS APPLICATION TO GENETIC STUDIES

Whole-genome gene expression profiling, or transcriptomics, is a robust approach toward the quantitative and qualitative characterization of RNA expressed in a biological system. Since the development of synthetic oligonucleotide microarray platforms in 2003,⁶⁷ 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.⁶⁸

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 with older microarray technology because of its smaller technical variation⁶⁹ and higher correlation with protein expression.⁷⁰ RNA-Seq has virtually unlimited dynamic range and permits digital quantification of transcript abundance, assessment of transcript isoforms, and alternative splicing,^{71–73} and it allows for unbiased assembly of transcripts without relying on previous annotation (including noncoding 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 with nonasthmatics⁷⁴ and the identification of genes differentially expressed in response to glucocorticosteroid exposure (*CRISPLD2*,⁷⁵ *FAM129A* and *SYNPO2*⁷⁶).

Although it is ideal to measure the transcriptome of a primary cell specific to the disease of interest (ie, 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 (ie, lung tissue), which have the potential to significantly move the field forward. For example, Poole and colleagues⁷⁷ 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 with healthy controls, and these changes are reflected by differential expression in the bronchial airway.

Differential gene expression in people is heritable,^{78,79} and GWAS of gene expression is an innovative approach for mapping functional noncoding 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,^{80,81} which can result in a gain in power.⁸² 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),^{83–85} 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 colleagues⁸¹ 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, an SNP in the chr. 17q21 region. Murphy and colleagues⁸⁶ identified common genetic variants influencing expression of 1585 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 6706 *cis*-acting expression-associated variants (eSNPs) from a genome-wide eQTL survey of CD4+ T cells from asthmatics, the *ORMDL3/GSDMB* locus held up ($P = 2.9 \times 10^{-8}$).⁸⁷

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).^{88–91} Furthermore, bronchial asthma was found to be the most common cause of cough in a small cohort of SLE patients from Bangladesh⁹² and Taiwan.⁹³ In addition, the inflammatory gene tumor necrosis factor α (TNF α) was found to be a common genetic risk factor for asthma, and autoimmune diseases juvenile rheumatoid arthritis (JRA) and SLE.⁹⁴ In a more recent study, PCR-based genotyping identified 4 *FCRL3* single nucleotide polymorphisms associated with protection in either 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 immunologic pathologies including RA, acute lung injury, asthma, and emphysema,⁹⁵ 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.^{96,97} Recently, Hardin and colleagues⁹⁸ 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 (ie, *GPR65*) unique to this subphenotype. Finally, there is a large body of research associated with the hygiene hypothesis⁹⁹ addressing the

potential beneficial role of microbial exposures for later development of asthma and allergies. Specifically, the underlying immunologic mechanisms and the type of infectious/microbial stimuli relevant to helminth infection (ie, schistosomiasis) are the same mechanisms that promote the Th2-mediated response in allergic disease,^{100,101} and common genetic mechanisms that underlie both schistosomiasis and asthma have been reported from linkage and candidate gene studies.¹⁰¹

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 pathologic mechanisms of disease.¹⁰² Such data-dense technologies include: DNA in the context of complete genomics; gene regulation technologies (epigenomics); global protein and/or post-transcriptional modifications (proteomics); and all cellular metabolites (metabolomics).¹⁰³

Transcriptomics extended to micro-RNA is another burgeoning field. Several micro-RNA have been identified as distinct profiles for the development and status of asthma, as well as other allergic phenotypes.^{104,105} Approximately 200 micro-RNA are known to be altered in steroid-naïve asthmatics, establishing a link between abnormal micro-RNA expression in asthmatic patients and inflammation.^{106–108} High-throughput data combined with sequence-based micro-RNA predictions have been successfully applied,^{109–113} and more recently, a transcriptome study on micro-RNA-long noncoding RNA interactions suggested better understanding of lung disease regulation and progression.¹¹⁴ 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.¹¹⁵

Concordance rates for asthma and allergies of only approximately 50% among monozygotic twins suggest differences in exposure to environmental triggers are critical in disease expression,^{2,116,117} and it has been demonstrated that genes and environmental factors contribute equally to asthma and its associated traits such as total Immunoglobulin E (tIgE).³ Similar to the other allergic diseases, the prevalence of asthma has increased dramatically within the 20 to 30 years in relation to the deterioration of the environment, favoring a significant contribution of environmental factors.¹¹⁸ 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, Arizona,¹¹⁹ but the opposite association was reported in a farming community.¹²⁰ 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,¹²¹ suggesting the role of endotoxin in allergic disease may be caused by 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,^{122–125} and ETS exposure increases strength of the association between markers in candidate genes and atopic asthma.^{126–128} 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.¹²⁹

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.¹³⁰ 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.¹³¹ A recent study found that DNA methylation in the β -2 adrenergic receptor (*ADRB2*) gene is associated with decreased asthma severity.¹³² 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.¹³³

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.¹³⁴ Epigenomics allows for the study of gene regulation at the chromosomal level using DNA methylation and chromatin immunoprecipitation (CHIP) technologies. As an example, 870 genes are differentially methylated in idiopathic pulmonary fibrosis (IPF) tissues,¹³⁵ and changes in micro-RNA and fibroblast signature for genes are known to regulate the extracellular matrix in IPF.^{136,137} 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.¹³⁸

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 immunoglobulin E (IgE) levels, resulting in structural remodeling and hyper-responsiveness consistent with allergic disease. In addition, mice that received HDM exposure had global changes in methylation and hydroxymethylation of approximately 213 genes, with *TGF β 2* and *SMAD3* having the most connected network.¹³⁹ These findings demonstrate how allergen exposure could trigger epigenetic changes in the lung genome.

CLINICAL IMPLICATIONS AND 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 adverse effects. For example, despite the relative success of conventional asthma therapies such as inhaled beta agonists and glucocorticoids, most cause adverse side effects^{140–142} and a subset of asthmatics are refractory to anti-asthma therapies resulting in significant morbidity as well as a significant financial burden.^{143–145} Genetic variation determines drug response through various mechanisms including pharmacodynamics mechanisms, which determine drug metabolism.¹⁴⁶

Recent GWAS and studies of candidate genes related to the β 2-adrenergic receptor pathway have attempted to identify specific variants associated with the response to inhaled beta agonists.^{147–149} The Arg¹⁶ allele in *ADRB2* has been associated with greater postbronchodilator forced expiratory volume in 1 minute (FEV1) response to short-acting beta agonists (SABA) asthma therapy in asthmatic children,^{150,151} while the Gly¹⁶ variant has been associated with changes in peak flow rate (PEFR).^{152–154}

In contrast, the Arg¹⁶ allele has been associated with worsening asthma symptom scores with long-acting beta agonist (LABA) therapy compared with Gly¹⁶ homozygotes.¹⁵⁵ Other studies show no difference between the *ADRB2* alleles and asthma symptoms after LABA therapy.^{156,157} Further pharmacogenetic studies may achieve a more definitive characterization of the role of Gly¹⁶Arg after beta agonist exposure and determine whether receptor kinetics or proinflammatory 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*¹⁴⁹ and *ARG1*¹⁵⁸ with FEV1 change, and *CRH2*¹⁴⁷ and *SPATS2L*¹⁴⁸ with bronchodilator response. Additional candidate gene studies have also demonstrated altered asthma phenotypes in response to glucocorticoid therapies including *CRH1*,¹⁵⁹ *STIP1*,¹⁶⁰ *TBX21*,^{161,162} *ADCY9*,^{149,163} and *ORDML3*.¹⁶⁴

FUTURE CONSIDERATIONS/SUMMARY

Although 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. Although the vast amount of genomic data that are now available for a plethora of complex diseases, including allergic disease, have facilitated follow-up association analyses to explore new hypotheses, meta-analyses, and replication of novel findings,¹⁶⁵ the scientific community is facing a big data crisis,¹⁶⁶ 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.¹⁶⁷ Consider that, in the field of pharmacogenetics, it has been 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.^{168,169} 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 multidisciplinary approach, attributes that have already pushed the genetics of allergic disease into the genomic revolution, with promises of improved outcome for the patient.

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APPENDIX A: A SUMMARY OF GENOME-WIDE ASSOCIATION STUDIES (GWAS) PERFORMED ON ALLERGIC DISEASES (P -VALUES ON THE DISCOVERY SAMPLE $P < 10^{-5}$)

Population	Location	Reported Gene	Adjacent Gene (L, R)	References
Asthma				
European	1p13.1	<i>IGSF3</i>	<i>CD58, MIR320B1</i>	Ding et al, ¹ 2013
European	1q25.3	<i>XPR1</i>	<i>ACBD6, KIAA1614</i>	Ding et al, ¹ 2013
European	1q44	<i>C1orf100</i>	<i>CEP170, HNRNPU</i>	Forno et al, ² 2012
European	1q21.3	<i>IL6R</i>	<i>SHE, LOC101928101</i>	Ferreira et al, ³ 2011
Mixed ethnicities	1q23.1	<i>PYHIN1</i>	<i>IFI16, LOC646377</i>	Torgerson et al, ⁴ 2011
Mixed ethnicities	1q21.3	<i>CRCT1</i>	<i>LCE5A, LCE3E</i>	Torgerson et al, ⁴ 2011
European	1q31.3	<i>DENND1B</i>	<i>CRB1, C10rf53</i>	Sleiman et al, ⁵ 2010
Korean	2p22.2	<i>CRIM1</i>	<i>LOC10028911, FEZ2</i>	Kim et al, ⁶ 2013
Korean	2q36.2	<i>DOCK10</i>	<i>CUL3, MIR4439</i>	Kim et al, ⁶ 2013
European	2p22.1	<i>Intergenic</i>	<i>THUMPD2, SLC8A1-AS1</i>	Ding et al, ¹ 2013
European	2q34	<i>CPS1</i>	<i>LOC102724820, ERBB4</i>	Melen et al, ⁷ 2013
European	2p23.3	<i>ADCY3</i>	<i>NCOA1, DNAJC27-AS1</i>	Melen et al, ⁷ 2013
European	2p23.3	<i>ADCY3</i>	<i>PTRHD1, DNAJC27</i>	Melen et al, ⁷ 2013
European	2p23.3	<i>EFR3B</i>	<i>DNAJC27, DNMT3A</i>	Melen et al, ⁷ 2013
European	2p23.3	<i>Intergenic</i>	<i>ADCY3, DNAJC27</i>	Melen et al, ⁷ 2013
European	2q12.1	<i>IL1RL1</i>	<i>IL1R1, IL18RAP</i>	Ramasamy et al, ⁸ 2012
European	2q33.1	<i>SPATS2L</i>	<i>TYW5, SGOL2</i>	Himes et al, ⁹ 2012
European	2q12.1	<i>IL1RL1, IL18R1</i>	<i>IL1R2, IL18RAP</i>	Wan et al, ¹⁰ 2012
Mixed ethnicities	2q12.1	<i>IL1RL1</i>	<i>IL1R1, IL18RAP</i>	Torgerson et al, ⁴ 2011
European	2q12.1	<i>IL18R1</i>	<i>IL1RL1, IL18RAP</i>	Moffatt et al, ¹¹ 2010
European	3q13.2	<i>ATG3</i>	<i>BTLA, SLC3A5</i>	Ding et al, ¹ 2013
European	3p22.3	<i>Intergenic</i>	<i>LOC101928135, ARPP21</i>	Ding et al, ¹ 2013
European	3q26.32	<i>Intergenic</i>	<i>LOC102724550, KCNB2</i>	Ding et al, ¹ 2013
European	3q12.2	<i>ABI3BP</i>	<i>TFG, IMPG2</i>	Ding et al, ¹ 2013
European	3p26.2	<i>IL5RA</i>	<i>CNTN4, LRRN1</i>	Forno et al, ² 2012
Korean	4q26	<i>SYNPO2</i>	<i>SEC24D, MYOZ2</i>	Kim et al, ⁶ 2013
European	4q12	<i>Intergenic</i>	<i>IGFBP7, LPHN3</i>	Ding et al, ¹ 2013
European	4p14	<i>KLHL5</i>	<i>TMEM156, WDR19</i>	Ding et al, ¹ 2013
European	4p15.1	<i>Intergenic</i>	<i>PCDH7, ARAP2</i>	Melen et al, ⁷ 2013
Japanese	4q31.21	<i>LOC729675</i>	<i>INPP4B, USP38</i>	Hirota et al, ¹² 2011
Japanese	4q31.21	<i>GAB1</i>	<i>USP38, SMARCA5</i>	Hirota et al, ¹² 2011
European	5q31.1	<i>C5orf56</i>	<i>SLC22A5, IRF1</i>	Wan et al, ¹⁰ 2012
European	5q31.3	<i>NDFIP1</i>	<i>GNPDA1, NDFIP1</i>	Wan et al, ¹⁰ 2012
Japanese	5q22.1	<i>TSLP</i>	<i>SLC25A46, WDR36</i>	Hirota et al, ¹² 2011
Mixed ethnicities	5q22.1	<i>TSLP</i>	<i>SLC25A46, WDR36</i>	Torgerson et al, ⁴ 2011

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Population	Location	Reported Gene	Adjacent Gene (L, R)	References
European	5q31.1	<i>SLC22A5</i>	<i>LOC553103, C5orf56</i>	Moffatt et al, ¹¹ 2010
European	5q31.1	<i>IL13</i>	<i>RAD50, IL4</i>	Moffatt et al, ¹¹ 2010
European	5q31.1	<i>RAD50</i>	<i>IL5, IL13</i>	Li et al, ¹³ 2010
European	5q12.1	<i>PDE4D</i>	<i>RAB3C, PART1</i>	Himes et al, ¹⁴ 2009
European	6p21.1	<i>Intergenic</i>	<i>CDC5L, SUPT3H</i>	Ding et al, ¹ 2013
European	6q21	<i>Intergenic</i>	<i>RFPL4B, LINC01268</i>	Ding et al, ¹ 2013
European	6p12.3	<i>AL139097.1</i>	<i>TFA2B, PKHD1</i>	Melen et al, ⁷ 2013
European	6p21.32	<i>HLA-DQA1</i>	<i>HLA-DRB1, HLA-DQB1</i>	Lasky-Su et al, ¹⁵ 2012
Korean	6p21.32	<i>HLA-DPB1</i>	<i>HLA-DPA1, HLA-DPB2</i>	Park et al, ¹⁶ 2013
European	6p21.32	<i>BTNL2</i>	<i>HCG23, HLA-DRA</i>	Ramasamy et al, ⁸ 2012
European	6q27	<i>T</i>	<i>LINC00602, PRR18</i>	Tantisira et al, ¹⁷ 2012
Japanese	6p21.32	<i>PBX2</i>	<i>AGER, GP5M3</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>NOTCH4</i>	<i>GP5M2, C6orf10</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>C6orf10</i>	<i>NOTCH4, HCG23</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>BTNL2</i>	<i>HCG23, HLA-DRA</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>HLA-DRA</i>	<i>BTNL2, HLA-DRB5</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>HLA-DQB1</i>	<i>HLA-DQA1, HLA-DQA2</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>HLA-DQA2</i>	<i>HLA-DQB1, HLA-DQB2</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>HLA-DOA</i>	<i>BRD2, HLA-DPA1</i>	Hirota et al, ¹² 2011
Japanese	6p21.32	<i>HLA-DPB1</i>	<i>HLA-DPA1, HLA-DPB2</i>	Noguchi et al, ¹⁸ 2011
European	6p21.32	<i>HLA-DQB1</i>	<i>HLA-DQA1, HLA-DQA2</i>	Moffatt et al, ¹¹ 2010
European	7p15.3	<i>Intergenic</i>	<i>NPY, STK31</i>	Ding et al, ¹ 2013
European	7q32.3	<i>MKLN1</i>	<i>LINC-PINT, PODXL</i>	Ding et al, ¹ 2013
Korean	8q11.23	<i>OPRK1</i>	<i>NPBWR1, ATP6V1H</i>	Kim et al, ⁶ 2013
European	8p12	<i>Intergenic</i>	<i>DUSP26, UNC5D</i>	Ding et al, ¹ 2013
European	8q24.23	<i>COL22A1</i>	<i>FAM135B, KCNK9</i>	Duan et al, ¹⁹ 2014
Japanese	8q24.11	<i>SLC30A8</i>	<i>AARD, MED30</i>	Noguchi et al, ¹⁸ 2011
Korean	9p13.3	<i>TLN1</i>	<i>TPM2, MIR6852</i>	Kim et al, ⁶ 2013
European	9p23	<i>Intergenic</i>	<i>PTPRD-AS2, TYRP1</i>	Ding et al, ¹ 2013
European	9q21.33	<i>Intergenic</i>	<i>ZCCHC6, GAS1</i>	Ding et al, ¹ 2013
European	9p22.1	<i>SLC24A2</i>	<i>ACER2, MLLT3</i>	Melen et al, ⁷ 2013
European	9q33.3	<i>DENND1A</i>	<i>CRB2, LHX2</i>	Melen et al, ⁷ 2013
European	9p21.1	<i>ACO1</i>	<i>LINC01242, DDX58</i>	Wan et al, ¹⁰ 2012
Mixed ethnicities	9p24.1	<i>IL33</i>	<i>RANBP6, TPD52L3</i>	Torgerson et al, ⁴ 2011
European	9p24.1	<i>IL33</i>	<i>RANBP6, TPD52L3</i>	Moffatt et al, ¹¹ 2010
Mexican	9q21.31	<i>TLE4, CHCHD9</i>	<i>LOC101927450, LOC101927477</i>	Hancock et al, ²⁰ 2009
Korean	9p21.3	<i>Intergenic</i>	<i>SLC24A2, MLLT3</i>	Kim et al, ²¹ 2009
European	10q24.2	<i>HPSE2</i>	<i>HPS1, CNM1</i>	Ding et al, ¹ 2013
European	10q22.1	<i>PSAP</i>	<i>CDH23, CHST3</i>	Ding et al, ¹ 2013
European	10p15.1	<i>PRKCQ</i>	<i>LOC399715, PRKCQ-AS1</i>	Melen et al, ⁷ 2013

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Population	Location	Reported Gene	Adjacent Gene (L, R)	References
European	10q26.11	<i>EMX2</i>	<i>PDZD8, RAB11FIP2</i>	Li et al, ²² 2013
European	10p15.1	<i>PRKCQ</i>	<i>LOC101927964, LINC00702</i>	Duan et al, ¹⁹ 2014
European	10q21.1	<i>PRKG1</i>	<i>A1CF, PRKG1-AS1</i>	Ferreira et al, ³ 2011
Japanese	10p14	<i>LOC338591</i>	<i>LINC00708, LOC101928272</i>	Hirota et al, ¹² 2011
Korean	10q21.3	<i>CTNNA3</i>	<i>LOC101928913, LRRTM3</i>	Kim et al, ²¹ 2009
Korean	11q24.1	<i>OR6X1</i>	<i>ZNF202, OR6M1</i>	Kim et al, ⁶ 2013
European	11q13.4	<i>P2RY2</i>	<i>FCHSD2, P2RY2</i>	Melen et al, ⁷ 2013
European	11q24.2	<i>NR</i>	<i>LOC101929497, ETS1</i>	Forno et al, ² 2012
European	11q13.5	<i>LRRC32</i>	<i>C11orf30, GUCY2EP</i>	Ferreira et al, ³ 2011
Mixed ethnicities	11q23.2	<i>C11orf71</i>	<i>LOC101928940, RBM7</i>	Torgerson et al, ⁴ 2011
Japanese	12q13.2	<i>CDK2</i>	<i>PMEL, RAB5B</i>	Hirota et al, ¹² 2011
Japanese	12q13.2	<i>IKZF4</i>	<i>SUOX, RPS26</i>	Hirota et al, ¹² 2011
European	13q13.1	<i>STARD13, RP11-81F11.3</i>	<i>KL, RFC3</i>	Melen et al, ⁷ 2013
European	13q13.3	<i>NR</i>	<i>MIR548F5, DCLK1</i>	Forno et al, ² 2012
European	13q21.31	<i>PCDH20</i>	<i>MIR3169, LINC00358</i>	Ferreira et al, ³ 2011
Korean	13q12.13	<i>Intergenic</i>	<i>GPR12, USP12</i>	Kim et al, ²¹ 2009
Korean	14q32.2	<i>LOC730217</i>	<i>C14orf64, C14orf177</i>	Kim et al, ⁶ 2013
European	15q22.33	<i>SMAD3</i>	<i>SMAD6, AAGAB</i>	Moffatt et al, ¹¹ 2010
European	15q22.2	<i>RORA</i>	<i>LOC101928784, VPS13C</i>	Moffatt et al, ¹¹ 2010
European	15q21.2	<i>SCG3</i>	<i>DMXL2, LYSMD2</i>	Li et al, ¹³ 2010
Korean	16q23.3	<i>CDH13</i>	<i>MPH0SPH6, MLYCD</i>	Kim et al, ⁶ 2013
European	17q21.32	<i>Intergenic</i>	<i>MIR196A1, PRAC1</i>	Melen et al, ⁷ 2013
European	17q21.32	<i>Intergenic</i>	<i>MIR196A1, PRAC1</i>	Melen et al, ⁷ 2013
European	17q12	<i>ORMDL3</i>	<i>GSDMB, LRRC3C</i>	Wan et al, ¹⁰ 2012
European	17p12	<i>NR</i>	<i>HS3ST3A1, COX10-AS1</i>	Forno et al, ² 2012
Mixed ethnicities	17q12	<i>GSDMB</i>	<i>ZPBP2, ORMDL3</i>	Torgerson et al, ⁴ 2011
European	17q12	<i>ORMDL3</i>	<i>GSDMB, LRRC3C</i>	Ferreira et al, ²³ 2011
European	17q12	<i>GSDMB</i>	<i>ZPBP2, ORMDL3</i>	Moffatt et al, ¹¹ 2010
European	17q21.1	<i>GSDMA</i>	<i>LRRC3C, PSMD3</i>	Moffatt et al, ¹¹ 2010
European	17q12	<i>ORMDL3</i>	<i>GSDMB, LRRC3C</i>	Moffatt et al, ¹¹ 2010
European	18p11.31	<i>LPIN2</i>	<i>EMILIN2, MYOM1</i>	Melen et al, ⁷ 2013
European	18p11.32	<i>YES1</i>	<i>ENOSF1, ADCYAP1</i>	Li et al, ²² 2013
Korean	19q13.43	<i>ZNF71</i>	<i>ZNF470, SMIM17</i>	Kim et al, ⁶ 2013
European	19p13.11	<i>IL12RB1</i>	<i>AARDC2, MAST3</i>	Li et al, ²² 2013
European	19q13.42	<i>ZNF665</i>	<i>ZNF347, ZNF818P</i>	Wan et al, ¹⁰ 2012
European	20p12.3	<i>Intergenic</i>	<i>MIR8062, HA01</i>	Ding et al, ¹ 2013

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Population	Location	Reported Gene	Adjacent Gene (L, R)	References
European	20q13.2	<i>Intergenic</i>	<i>LOC101927700, TSHZ2</i>	Melen et al, ⁷ 2013
European	20p13	<i>KIAA1271</i>	<i>AP5S1, MAVS</i>	Li et al, ¹³ 2010
European	22q13.31	<i>UPK3A</i>	<i>NUP50, FAM118A</i>	Li et al, ²² 2013
European	22q12.3	<i>IL2RB</i>	<i>TMPRSS6, C1QTNF6</i>	Moffatt et al, ¹¹ 2010
European	NR	<i>Intergenic</i>		Wan et al, ¹⁰ 2012
Atopic Dermatitis				
European	1q21.3	<i>FLG</i>	<i>HRNR, FLG2</i>	Weidinger et al, ²⁴ 2013
Chinese	1q21.3	<i>FLG</i>	<i>HRNR, FLG2</i>	Sun et al, ²⁵ 2011
Japanese	2q12.1	<i>IL1RL1, IL18R1, IL18RAP</i>	<i>IL1R1, IL18RAP, IL1R2</i>	Hirota et al, ²⁶ 2012
Japanese	2q13	<i>LOC100505634</i>	<i>BCL2L11, MIR4435-1</i>	Hirota et al, ²⁶ 2012
Japanese	3p22.3	<i>GLB1</i>	<i>CCR4, SUSD5</i>	Hirota et al, ²⁶ 2012
Japanese	3q13.2	<i>CCDC80</i>	<i>LINC01279, LOC101929694</i>	Hirota et al, ²⁶ 2012
European	5q31.1	<i>IL13</i>	<i>RAD50, IL4</i>	Weidinger et al, ²⁴ 2013
Japanese	5q31.1	<i>IL13</i>	<i>RAD50, IL4</i>	Hirota et al, ²⁶ 2012
European	5q31.1	<i>IL13</i>	<i>RAD50, IL4</i>	Paternoster et al, ²⁷ 2012
European	6p21.33	<i>TNXB</i>	<i>CYP21A2, ATF6B</i>	Weidinger et al, ²⁴ 2013
Japanese	6p21.33	<i>HLA-C</i>	<i>HCG27, HLA-B</i>	Hirota et al, ²⁶ 2012
Japanese	6p21.32	<i>GPSM3</i>	<i>PBX2, NOTCH4</i>	Hirota et al, ²⁶ 2012
Japanese	6p21.32	<i>C6orf10</i>	<i>NOTCH4, HCG23</i>	Hirota et al, ²⁶ 2012
European	6p21.33	<i>BAT1</i>	<i>MCCD1, DDX39B</i>	Paternoster et al, ²⁷ 2012
Japanese	7p22.2	<i>CARD11</i>	<i>GNA12, SDK1</i>	Hirota et al, ²⁶ 2012
Japanese	8q24.21	<i>MIR1208</i>	<i>PVT1, LINC00977</i>	Hirota et al, ²⁶ 2012
European	8q21.13	<i>ZBTB10</i>	<i>MIR5708, ZNF704</i>	Paternoster et al, ²⁷ 2012
Japanese	10q21.2	<i>ZNF365</i>	<i>LOC283045, EGR2</i>	Hirota et al, ²⁶ 2012
Japanese	10q21.3	<i>ADO, EGR2</i>	<i>ZNF365, NRBF2</i>	Hirota et al, ²⁶ 2012
European	11q13.5	<i>C11orf30</i>	<i>LOC100506127, LRRC32</i>	Weidinger et al, ²⁴ 2013
Japanese	11p15.4	<i>OR10A3, NLRP10</i>	<i>OR10A3, NLRP10</i>	Hirota et al, ²⁶ 2012
Japanese	11q13.5	<i>C11orf30</i>	<i>LOC100506127, LRRC32</i>	Hirota et al, ²⁶ 2012
Japanese	11q13.1	<i>OVOL1</i>	<i>AP5B1, SNX32</i>	Hirota et al, ²⁶ 2012
European	11q13.1	<i>OVOL1</i>	<i>AP5B1, SNX32</i>	Paternoster et al, ²⁷ 2012
European	11q13.5	<i>C11orf30</i>	<i>LOC100506127, LRRC32</i>	Esparza-Gordillo et al, ²⁸ 2009
Japanese	16p13.13	<i>CLEC16A</i>	<i>DEXI, SOCS1</i>	Hirota et al, ²⁶ 2012
European	19p13.2	<i>ACTL9</i>	<i>ADAMTS10, OR2Z1</i>	Paternoster et al, ²⁷ 2012
Japanese	20q13.2	<i>CYP24A1, PFDN4</i>	<i>CYP24A1, PFDN4</i>	Hirota et al, ²⁶ 2012
European	22q12.3	<i>NCF4</i>	<i>PVALB, CSF2RB</i>	Paternoster et al, ²⁷ 2012

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Population	Location	Reported Gene	Adjacent Gene (L, R)	References
Atopy				
European	2p21	<i>SGK493</i>	<i>C2orf91, PKDCC</i>	Castro-Giner et al, ²⁹ 2009
Allergic Rhinitis				
European	1p36.13	<i>CROCC</i>	<i>MIR3675, MFAP2</i>	Ramasamy et al, ³⁰ 2011
European	5q22.1	<i>TMEM232, SLC25A46</i>	<i>LOC100289673, TSLP</i>	Ramasamy et al, ³⁰ 2011
European	5q22.1	<i>TSLP</i>	<i>SLC25A46, WDR36</i>	Ramasamy et al, ³⁰ 2011
European	5q23.1	<i>SEMA6A</i>	<i>LOC101927190, LOC102467223</i>	Ramasamy et al, ³⁰ 2011
European	7p14.1	<i>GLI3</i>	<i>INHBA-AS1, LINC01448</i>	Ramasamy et al, ³⁰ 2011
European	11q13.5	<i>C11orf30, LRRC32</i>	<i>LOC100506127, GUCY2EP</i>	Ramasamy et al, ³⁰ 2011
European	14q23.1	<i>PPM1A, DHRS7</i>	<i>PCNXL4, C14orf39</i>	Ramasamy et al, ³⁰ 2011
European	16p13.13	<i>CLEC16A</i>	<i>DEXI, SOCS1</i>	Ramasamy et al, ³⁰ 2011
European	20p11.21	<i>ENTPD6</i>	<i>LOC101926889, PYGB</i>	Ramasamy et al, ³⁰ 2011
Total and Specific Immunoglobulin E				
European	1p32.3	<i>EPS15</i>	<i>TTC39A, OSBPL9</i>	Ramasamy et al, ³⁰ 2011
European	1q23.2	<i>DARC</i>	<i>CADM3-AS1, ACKR1</i>	Granada et al, ³¹ 2012
European	1q23.2	<i>FCER1A</i>	<i>ACKR1, OR10J3</i>	Weidinger et al, ³² 2008
European	1q23.2	<i>FCER1A</i>	<i>Mus Olfr418-ps1, OR10J3</i>	Granada et al, ³¹ 2012
European	1q23.2	<i>OR10J3</i>	<i>FCER1A, OR10J1</i>	Granada et al, ³¹ 2012
European	1q25.2	<i>ABL2</i>	<i>TOR3A, SOAT1</i>	Ramasamy et al, ³⁰ 2011
Korean	2p22.2	<i>CRIM1</i>	<i>LOC100288911, FEZ2</i>	Kim et al, ⁶ 2013
European	2p25.1	<i>ID2</i>	<i>LOC100506299, MBOAT2</i>	Granada et al, ³¹ 2012
Korean	2q36.2	<i>DOCK10</i>	<i>CUL3, NYAP2</i>	Kim et al, ⁶ 2013
Mixed ethnicities	3p14.1	<i>SUCLG2</i>	<i>MIR4272, SUCLG2-AS1</i>	Levin et al, ³³ 2013
European	3q22.1	<i>TMEM108</i>	<i>NPHP3-AS1, BFSP2</i>	Ramasamy et al, ³⁰ 2011
European	3q28	<i>LPP</i>	<i>BCL6, TPRG1-AS1</i>	Granada et al, ³¹ 2012
Korean	4q26	<i>SYNPO2</i>	<i>SEC240, MYOZ2</i>	Kim et al, ⁶ 2013
European	4q27	<i>IL2</i>	<i>ADAD1, IL21</i>	Ramasamy et al, ³⁰ 2011
European	5p15.2	<i>DNAH5</i>	<i>LINC01194, TRIO</i>	Ramasamy et al, ³⁰ 2011
European	5q22.1	<i>TMEM232, SLC25A46</i>	<i>LOC100289673, TSLP</i>	Ramasamy et al, ³⁰ 2011
European	5q31.1	<i>IL13</i>	<i>BC042122, IL4</i>	Granada et al, ³¹ 2012
European	5q31.1	<i>RAD50</i>	<i>IL5, IL13</i>	Weidinger et al, ³² 2008
European	6p21.32	<i>HLA region</i>	<i>HLA-DQB1, HLADQA2</i>	Ramasamy et al, ³⁰ 2011
European	6p21.32	<i>HLA-DQA2</i>	<i>HLA-DQB1, HLA-DQB2</i>	Granada et al, ³¹ 2012
Mixed ethnicities	6p21.32	<i>HLA-DQA2</i>	<i>HLA-DQB1, HLA-DQB2</i>	Levin et al, ³³ 2013

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Population	Location	Reported Gene	Adjacent Gene (L, R)	References
Mixed ethnicities	6p21.32	<i>HLA-DQB1</i>	<i>HLA-DQA1, HLA-DQA2</i>	Levin et al, ³³ 2013
European	6p22.1	<i>HLA-G</i>	<i>LOC554223, HLA-H</i>	Granada et al, ³¹ 2012
European	6p22.1	<i>HLA-A</i>	<i>HCG4B, HCG9</i>	Granada et al, ³¹ 2012
Korean	8q11.23	<i>OPRK1</i>	<i>NPBWR1, ATP6V1H</i>	Kim et al, ⁶ 2013
Korean	9p13.3	<i>TLN1</i>	<i>TPM2, CREB3</i>	Kim et al, ⁶ 2013
Korean	11q24.1	<i>OR6X1</i>	<i>ZNF202, ORM1</i>	Kim et al, ⁶ 2013
European	12q13.3	<i>STAT6, NAB2</i>	<i>TMEM194A, LRP1</i>	Granada et al, ³¹ 2012
Korean	14q32.2	<i>LOC730217</i>	<i>C14orf64, C14orf177</i>	Kim et al, ⁶ 2013
European	16p12.1	<i>IL4R</i>	<i>FLJ21408, IL21R</i>	Granada et al, ³¹ 2012
European	16p13.2	<i>Intergenic</i>	<i>MIR548X, MIR7641-2</i>	Ramasamy et al, ³⁰ 2011
Mixed ethnicities	16q22.1	<i>WWP2</i>	<i>NOB1, PDXDC2P</i>	Levin et al, ³³ 2013
Korean	16q23.3	<i>CDH13</i>	<i>MPHOSPH6, LOC102724163</i>	Kim et al, ⁶ 2013
Korean	19q13.43	<i>ZNF71</i>	<i>ZNF470, SMIM17</i>	Kim et al, ⁶ 2013
Airway Hyper-responsiveness				
European	2q36.3	<i>AGFG1</i>	<i>TM4SF20, C2orf83</i>	Himes et al, ³⁴ 2013
Mixed ethnicities = African American/African Caribbean, Latino, European ancestry				

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