



Discovering susceptibility genes for allergic rhinitis and allergy using a genome-wide association study strategy

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Purpose of review

Allergic rhinitis and allergy are complex conditions, in which both genetic and environmental factors contribute to the pathogenesis. Genome-wide association studies (GWASs) employing common single-nucleotide polymorphisms have accelerated the search for novel and interesting genes, and also confirmed the role of some previously described genes which may be involved in the cause of allergic rhinitis and allergy. The aim of this review is to provide an overview of the genetic basis of allergic rhinitis and the associated allergic phenotypes, with particular focus on GWASs.

Recent findings

The last decade has been marked by the publication of more than 20 GWASs of allergic rhinitis and the associated allergic phenotypes. Allergic diseases and traits have been shown to share a large number of genetic susceptibility loci, of which *IL33/IL1RL1*, *IL-13-RAD50* and *C11orf30/LRRC32* appear to be important for more than two allergic phenotypes. GWASs have further reflected the genetic heterogeneity underlying allergic phenotypes.

Summary

Large-scale genome-wide association strategies are underway to discover new susceptibility variants for allergic rhinitis and allergic phenotypes. Characterization of the underlying genetics provides us with an insight into the potential targets for future studies and the corresponding interventions.

Keywords

allergic rhinitis, allergy, genetic susceptibility, genome-wide association study

INTRODUCTION

Allergic rhinitis is an allergen-specific immunoglobulin E (IgE)-mediated inflammatory disease of the nasal mucosa, characterized by sneezing, nasal itching, rhinorrhoea and nasal congestion. The prevalence of allergic rhinitis is high globally, including China [1], and increasing progressively. Although not a life-threatening disorder, allergic rhinitis adversely impacts the quality of life of the affected individuals, and imposes a socioeconomic burden on both the individual and the society alike.

Allergic rhinitis and allergy are complex conditions, in which interaction between genetic and environmental factors contribute to the pathogenesis of these conditions. Family linkage and candidate-gene studies [2,3] based on the positional cloning have demonstrated that a number of susceptibility genes, including immune relevant factors and regulators of the epithelial barrier, play a part in the cause of allergic rhinitis and allergy

phenotypes. However, the findings from these studies are neither consistent nor conclusive, because of the genetic heterogeneity. The elucidation of the human genome has enabled the study of genomic variation amongst individuals with specific conditions and led to the development of genome-wide association studies (GWASs) employing common

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KEY POINTS

- Genome-wide association studies (GWASs) have accelerated the search for novel genetic loci for allergic rhinitis and allergy.
- More than 20 GWASs of allergic rhinitis and allergic phenotypes have been published in the last decade.
- GWASs have shown that allergic diseases and traits share a large number of genetic susceptibility loci.
- GWASs also reflect the genetic heterogeneity underlying allergic phenotypes.

single-nucleotide polymorphisms (SNPs). The GWASs have thus both accelerated the search for novel and interesting genes, and confirmed the role of some previously described genes associated with the development of allergic rhinitis and allergy. The aim of this study is to review the current literature and provide an overview of the genetic basis of allergic rhinitis and other allergic phenotypes in relation to allergic rhinitis, with particular focus on GWASs.

GENOME-WIDE ASSOCIATION STUDIES OF ALLERGIC RHINITIS

Despite the high prevalence of allergic rhinitis, only three GWASs of allergic rhinitis have been reported to date (Table 1) [4,5,6[■],7[■],8,9[■],10–20,21[■],22–25,26[■]]. Andiappan *et al.* [4] first employed GWAS strategy to identify the genetic variants that influenced predisposition towards allergic rhinitis and atopy in a cohort of 4461 ethnic Chinese individuals in Singapore. The authors demonstrated that SNPs in two novel candidate genes, *MRPL4* (mitochondrial ribosomal protein L4) on chromosome 19p13.2 and *BCAP* (B-cell adaptor for phosphatidylinositol 3-kinase) on chromosome 10q24.1, were consistently associated with allergic rhinitis and atopy in both the discovery and validation phases of the GWAS. Moreover, multiple associations were also replicated within known candidate regions such as *HLA-DQ* and *NPSR1* locus in the discovery phase of the study. A recent study [27[■]] has investigated the associations of novel loci with allergic rhinitis in a Han Chinese population and demonstrated that SNPs in not only the *MRPL4* gene, but also the *TNF-α* gene was strongly associated with the risk of allergic rhinitis. Indeed, the 19p13.2 locus has previously been reported to influence the levels of soluble intercellular adhesion molecule 1, which is a key regulator of nasal allergic reaction [28].

A recent large-scale, meta-based GWAS of allergic rhinitis investigated approximately 2.2 million

genotyped or imputed SNPs in four large European adult cohorts for allergic rhinitis in a total of 3933 self-reported seasonal allergic rhinitis patients vs. 8965 control individuals, as well as for grass sensitization in 2315 cases vs. 10032 control individuals [5]. Three loci, including the HLA variant rs7775228, variants near chromosome 11 open-reading frame 30 (*C11orf30*) and leucine-rich repeat containing 32 (*LRRC32*), and variant rs2155219, reached genome-wide significance for both phenotypes. Of these, the variants within chromosome 11q13 were strongly associated with allergic rhinitis. Interestingly, these variants have also been shown to be associated with increased risk of atopic dermatitis and eczema as well as asthma [7[■],18]. *C11orf30* encodes the EMSY protein involved in epithelial barrier function via transcriptional repression [29], whereas *LRRC32* encodes a T-cell surface receptor for latent TGF-β and is essential for regulatory T-cell functions and immune tolerance [30].

A more recent study [6[■]] has integrated GWASs, coexpression network and expression SNP analysis of allergic rhinitis in 5633 ethnically diverse North American individuals to identify the biologic relevance of the findings from GWASs. The authors demonstrated that a locus on chromosome 7p21.1 near gene *FERD3L* (Fer3-like bHLH transcription factor) indicated genome-wide significance in the meta-analysis across all ethnic groups. Furthermore, the integrated approach involving pathway analysis revealed that the module was significantly enriched for mitochondrial pathways (8.6-fold enrichment), suggesting that mitochondrial pathways were likely to be important targets for future investigations of AR mechanisms and treatment [6[■]].

GENOME-WIDE ASSOCIATION STUDIES OF ASTHMA AND ATOPIC DERMATITIS IN RELATION TO ALLERGIC RHINITIS

Asthma, atopic dermatitis and allergic rhinitis are three common allergic diseases, which have similarities in cause, for example, elevated IgE, and which often coexist in the same family or patient [31,32]. Thus, it is likely that different allergic diseases may share overlapping genetic susceptibility.

The last decade has been marked by the publication of more than 10 GWASs in asthma and 5 GWASs for atopic dermatitis (Table 1). The first published GWAS of asthma, performed in 2007 by the GABRIEL (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) consortium [8], reported that the locus on chromosome 17q21, which includes genes *ORMDL3*, *GSDML*, *ZPBP2* and *IKZF3*, contribute to the susceptibility for onset of

Table 1. Susceptibility loci of allergic rhinitis, asthma and atopic dermatitis identified by GWASs

Allergic disease	Chromosome	Gene	Possible allergic mechanism	Reference
Allergic rhinitis	19p13	<i>MRPL4</i>	Involved in inflammatory adhesion process	[4]
	10q24	<i>BCAP</i>	Involved in activation, development and maturation of B cells	[4]
	11q13	<i>C11orf30/LRRC32</i>	Epithelial barrier function/regulatory T-cell functions and immune tolerance	[5]
Asthma	7p21	<i>FERD3L</i>	Unknown	[6 ^{***}]
	17q21	<i>ORMDL3/GSDML</i>	Involved in calcium homeostasis	[7 ^{***} ,8,9 ^{***} ,10,11]
			Regulation of sphingolipid metabolism	
	2q12	<i>IL1RL1/IL18R1</i>	Involved in Th2 responses	[7 ^{***} ,10–12]
	9p24	<i>IL-33</i>	Involved in Th2 responses	[7 ^{***} ,10,12]
	6p21	<i>HLA</i>	Involved in T-cell responses	[7 ^{***} ,10,13–16]
	15q22	<i>SMAD3</i>	Transcriptional modulator activated by TGF- β	[7 ^{***} ,10,12]
	22q12	<i>IL2RB</i>	Involved in T-cell-mediated immune responses	[10]
	5q22	<i>TSLP</i>	Activates dendritic cells, Th2 immune responses	[7 ^{***} ,12]
	5q31	<i>RAD50-IL-13</i>	DNA repair/a cluster of cytokine	[17]
	11q13	<i>C11orf30/LRRC32</i>	Epithelial barrier function/regulatory T-cell functions and immune tolerance	[7 ^{***} ,18]
	1q31	<i>DENND1B</i>	Expressed in dendritic cells and activates T cells	[19]
	4p14	<i>TLR6-TLR1</i>	Pathogen recognition and activation of innate immunity	[7 ^{***} ,18]
	1q21	<i>IL6R</i>	Regulatory T-cell functions	[18]
	5q12	<i>PDE4D</i>	Involved in the airway smooth muscle contractility	[20]
	7q22	<i>CDHR3</i>	Epithelial polarity, cell–cell contact	[9 ^{***}]
	8q21	<i>ZBTB10</i>	Sp1 transcription factor, regulates multiple immune-related genes	[7 ^{***}]
	16p13	<i>CLEC16A</i>	Inflammatory cell function	[7 ^{***}]
	1p31	<i>NFIA</i>	Controls monocyte/macrophage differentiation programme	[21 [■]]
	4q31	<i>USP38-GAB1</i>	Unknown/involved in IL-3, IL-6, interferon α and γ , and B-cell and T-cell receptors pathways	[22]
	10p14	<i>GATA3</i>	Master regulator of Th2 differentiation	[22]
	12q13	<i>IKZF4</i>	Involved in differentiation of regulatory T cells	[22]
Atopic dermatitis	1p21	<i>FLG</i>	Epidermal structure and function	[13,23–25,26 ^{***}]
	11q13	<i>C11orf30/LRRC32</i>	Epithelial barrier function/regulatory T-cell functions and immune tolerance	[23,25,26 ^{***}]
	5q22	<i>TMEM232 /SLC25A46</i>	Tetraspan protein/transporter	[13,24]
			Unknown	
	20q13	<i>TNFRSF6B /ZGPAT</i>	Decoy receptor 3, involved in airway remodelling/unknown	[13,24]
	5q31	<i>RAD50-IL-13-KIF3A</i>	DNA repair/a cluster of cytokine/cilia protein	[13,25,26 ^{***}]
	11q13	<i>OVOL1</i>	Epidermal proliferation and differentiation	[13,25]
	19p13	<i>ADAMTS10/ACTL9</i>	Epidermal proliferation and differentiation	[13,25]

Table 1 (Continued)

Allergic disease	Chromosome	Gene	Possible allergic mechanism	Reference
	2q12	<i>IL1RL1/IL18R1</i>	Involved in Th2 responses.	[13]
	6p21	<i>MHC region</i>	Autoimmunity	[13,26 ^{***}]
	11p15	<i>OR10A3-NLRP10</i>	Initiates adaptive immunity by dendritic cells	[13]
	3p21	<i>GLB1</i>	Unknown	[13]
	3q13	<i>CCDC80</i>	Keratinocytes differentiation	[13]
	7p22	<i>CARD11</i>	Scaffold protein for lymphocyte activation via T-cell receptor and B-cell receptor signalling	[14]
	10q21	<i>ZNF365/EGR2</i>	Unknown/negative regulation of T-cell proliferation and Inflammation	[13]
	20q13	<i>CYP24A1-PFDN4</i>	Mitochondrial cytochrome p450 superfamily enzyme/unknown	[13]

GWASs, genome-wide association studies.

childhood asthma. Subsequent replication studies [9^{***},10,11,33–35] indicated that variants on the *ORMDL3/GSDML* were associated with the risk of asthma in different ethnic populations. A recent study [36^{*}], employing linkage disequilibrium mapping techniques in two independent Japanese populations, demonstrated that variants in this locus were also associated with allergic rhinitis. In addition, the associated variants were correlated in cis with mRNA expression of *ORMDL3* in Epstein-Barr virus (EBV)-transformed lymphoblastoid cell lines from both an asthmatic child and patients with allergic rhinitis. Another recent large-scale, consortium-based GWAS for asthma, involving 10 365 asthmatic patients and 16 110 control individuals, has identified six asthma susceptible loci, including *IL1RL1/IL18R1*, *HLA-DQ*, *IL-33*, *SMAD3*, *IL2RB* and *ORMDL3/GSDML* [10]. Particularly, *IL33*, a ligand for *IL1RL1* and an important effector cytokine of type 2 T-helper responses [37], has been reported in several other GWASs of asthma [7^{***},9^{***},12]. Indeed, genetic variants in *IL33* and the levels of serum *IL-33* have also been shown to be associated with Japanese cedar pollinosis, the most common form of allergic rhinitis in Japan [38]. Similarly, whereas one recent meta-analysis of GWASs of asthma has reported *TSLP* (thymic stromal lymphopoietin), an important epithelial-cell-derived cytokine-inducing type 2 T-helper inflammation, to also be significantly associated with asthma [12], several other studies [5,7^{***},39] have demonstrated an association between variants in or near *TSLP* and allergic rhinitis. Likewise, *RAD50-IL-13* at 5q31.1 has been shown to be another hotspot locus in the GWAS of asthma [17]. This contains a cluster of cytokine and immune-related genes, such as *IL3*, *IL4*, *IL5*, *IL13*, *GM-CSF* and the *RAD50* gene (DNA repair protein

RAD50), and also suggested to be a candidate for the susceptibility to allergic rhinitis in different populations [40–42]. Additionally, some GWASs have indicated that *C11orf30/LRRC32* is an overlapping loci associated with both allergic rhinitis and asthma [7^{***},18].

As a result of the common occurrence of comorbidities, it is necessary to confirm whether the susceptibility loci are shared or specific according to the disease status defined by the presence of the two diseases versus the presence of only one disease. A recent GWAS identified 11 independent variants associated with the risk of having asthma with rhinitis, of which associations for two variants, *ZBTN10* and *CLEC16A*, were significant [7^{***}]. Evidence from a genome-wide linkage scan in 295 families enrolled in the French Epidemiological Study on the Genetics and Environment of Asthma (EGEA) has further indicated that the combined asthma and allergic rhinitis phenotype is significantly linked with a genetic variant in the flanking 5' untranslated region of the nuclear factor I/A (*NFIA*) gene in the 1p31 linkage region [21^{*},43].

To date, only five GWASs have been reported for atopic dermatitis (Table 1). The first GWAS of atopic dermatitis identified two genetic loci on chromosomes 1p21 and 11q13 [23], of which the 11q13 region encompassed *C11orf30/LRRC32*, as previously discussed for allergic rhinitis. Similarly, the 1p21 locus encompassed the *FLG* gene, which codes for the key protein filaggrin that facilitates terminal differentiation of the epidermis and formation of the skin barrier, and identified as a major susceptibility gene for atopic dermatitis [44]. Another GWAS of atopic dermatitis in the Chinese Han population identified two new susceptibility loci at 5q22.1 and 20q13.3 [24], of which locus 5q22.1 contained *TMEM232/SLC25A46*, which was

previously shown to be modestly associated with allergic rhinitis [5], and locus 20q13.3 contained *TNFRSF6B* gene, which was also identified in the largest GWAS of atopic dermatitis to date [25]. This GWAS of atopic dermatitis investigated two independent populations and identified five loci with genome-wide significance, including 1q21 (*FLG*), 5q31 (*KIF3A*), 11q13 (*OVOL1*), 19p13 (*ADAMTS10/ACTL9*) and 20q13 (*TNFRSF6B*) [25]. Interestingly, conditional logistic regression analysis showed that the association signal at locus 5q31.1, which has been associated with allergic rhinitis and asthma, appeared to consist of two independent signals: one located at *IL13-RAD50* and the other at *IL4-KIF3A*. Importantly, two recent GWASs have shown excellent replication for previously identified loci for atopic dermatitis, including *FLG*, *C11orf30/LRRC32*, *TNFRSF6B* and *KIF3A* [13,26^{***}].

GENOME-WIDE ASSOCIATION STUDIES OF ALLERGIC-RHINITIS-RELATED ENDOPHENOTYPES

Although GWASs of disease phenotype such as allergic rhinitis, asthma or atopic dermatitis have generally been successful in demonstrating the association between a genetic variant and a particular phenotype, GWASs investigating specific endophenotype or allergic quantitative traits have provided conclusive evidence regarding genetic regulation.

A common feature of allergic rhinitis and other allergic diseases is an IgE-mediated excessive immune responsiveness to environmental allergens, with many patients exhibiting increased total and allergen-specific IgE levels. The first GWAS of IgE serum levels in asthma patients identified associated variants mapping to *FCER1A* (alpha chain of the high-affinity receptor for IgE) at 1q23, *STAT6* at 12q13 and *IL-13-RAD50* at 5q31 region [45]. Subsequently, two GWASs confirmed the associations of these loci with serum IgE levels [10,46]. More recently, one study [47] has indicated that variants in *FCER1A* were associated with allergic diseases including asthma, allergic rhinitis and allergic sensitization defined by skin prick test (SPT).

Allergic rhinitis is strongly associated with allergic sensitization, defined by elevated levels of specific IgE. Although the first GWAS of allergic sensitization in a British 1958 Birth Cohort demonstrated that 13q14 (*FIND3A*) loci reached a genome-wide significant association with allergic sensitization, these findings have not been replicated in a larger independent population [48]. Recently, three meta-GWASs identified a set of 47 SNPs located in 37 loci, which were significantly associated with allergic sensitization [5,49^{***},50^{***}]. Furthermore, four

of these loci (*TLR6-TLR1*, *HLA-DQA2-HLA-DQA1*, *IL2-ADAD1* and *LRRC32-C11orf30*) were consistently demonstrated in all three studies, suggesting their potential relevance to allergic sensitization. A more recent study [51^{*}] has investigated the reproducibility of these loci in determining the associations between allergic sensitization and allergic rhinitis, and demonstrated that *TLR6-TLR1* was likely to play a central role in the development of allergic disease.

High blood eosinophil count is also an important feature of allergy. A GWAS for blood eosinophil counts has indicated the five loci, including 2q12 (*IL1RL1*), 2q34 (*IKZF2*), 3q21 (*GATA2*), 5q23 (*IL5*) and 12p24 (*SH2B3*), important in this respect [52], although these findings need to be confirmed in other studies.

OVERLAPPING LOCI IN THE GENOME-WIDE ASSOCIATION STUDIES OF ALLERGIC PHENOTYPES

Figure 1 shows that allergic diseases and traits share a large number of genetic susceptibility loci, of which *IL33/IL1RL1*, *IL-13-RAD50* and *C11orf30/LRRC32* appear to be important for more than two allergic phenotypes. These overlapping loci may partly explain the concept of 'atopic march', which proposes the progression of allergic disease from childhood atopic dermatitis to allergic rhinitis and asthma [53]. Thus, in individuals with atopic dermatitis, overlapping allergic genetic susceptibility would likely lead to an increased risk of developing asthma or allergic rhinitis. Indeed, one study [53] has indicated that about half of atopic dermatitis patients are likely to develop asthma and two-thirds develop allergic rhinitis. Similarly, the close relationship between allergic rhinitis and asthma and the finding that allergic rhinitis and asthma share the same genetic traits have led to the concept of 'the united airway' or 'one airway, one disease' [54]. Despite the overlapping genetic susceptibility to allergic diseases, genetic heterogeneity also plays an important role in determining the allergic phenotypes.

FUTURE RESEARCH

Although GWASs of allergic diseases have achieved great success in identifying genetic susceptibility loci, the identified variants have small effects with respect to the cause of diseases and explain little of the heritability. This 'missing heritability' phenomenon results from endophenotype confounding, unmapped common and rare variants, copy-number variations (CNV), epigenetic effects, gene-gene interactions and gene-environment interactions. For example, by defining the endotypes of asthma,

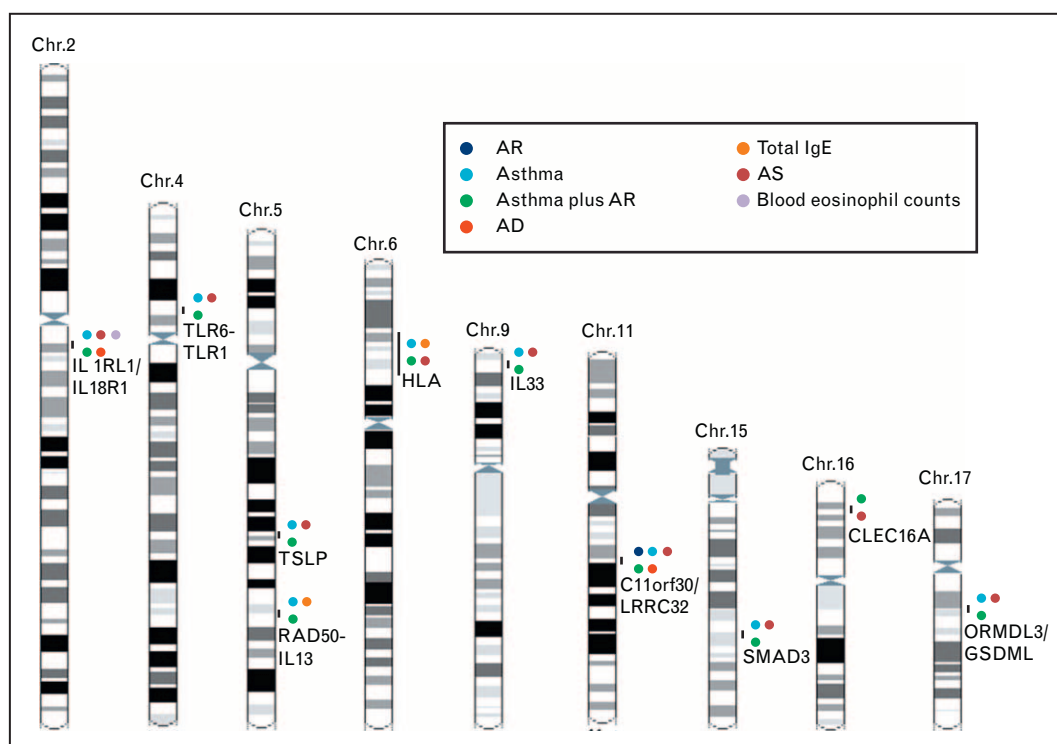


FIGURE 1. Overlapping loci in GWASs for allergic rhinitis (AR), asthma, asthma and AR, atopic dermatitis (AD), total IgE levels, allergic sensitization (AS) and blood eosinophil counts.

one GWAS has recently identified a new locus, *CDHR3*, associated with childhood severe asthma with exacerbation [9^{***}]. Additionally, exome sequencing and fine mapping of candidate loci via resequencing have discovered other important rare variants and CNV, which have biologic function [55,56].

Epigenetic modifications determine and mediate the environmental influences on gene expression [57], via the underlying epigenetic mechanisms which regulate the expression of key molecules or pathways in immunity related to the pathogenesis of allergic disorders [58,59]. Thus, promoter methylation, histone tail modification and noncoding RNAs may become candidate targets for genetic associations.

As translation of the biology of identified genetic changes is currently a major difficulty, Encyclopedia of DNA elements consortium (ENCODE) aims to identify the regulatory regions of the genome and expression of quantitative trait loci (eQTL) to provide further insight into the functional mechanisms.

CONCLUSION

Large-scale genome-wide association strategies are underway to discover new susceptibility variants for allergic rhinitis and allergic phenotypes. Characterization of the underlying genetics provides an

insight into the potential future study targets and corresponding interventions.

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Conflicts of interest

There are no conflicts of interest.

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