International Journal of General Medicine

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REVIEW

Genetic polymorphisms and associated susceptibility to asthma

This article was published in the following Dove Press journal:
International Journal of General Medicine
16 April 2013
Number of times this article has been viewed

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Abstract: As complex common diseases, asthma and allergic diseases are caused by the interaction of multiple genetic variants with a variety of environmental factors. Candidate-gene studies have examined the involvement of a very large list of genes in asthma and allergy, demonstrating a role for more than 100 loci. These studies have elucidated several themes in the biology and pathogenesis of these diseases. A small number of genes have been associated with asthma or allergy through traditional linkage analyses. The publication of the first asthma-focused genome-wide association (GWA) study in 2007 has been followed by nearly 30 reports of GWA studies targeting asthma, allergy, or associated phenotypes and quantitative traits. GWA studies have confirmed several candidate genes and have identified new, unsuspected, and occasionally uncharacterized genes as asthma susceptibility loci. Issues of results replication persist, complicating interpretation and making conclusions difficult to draw, and much of the heritability of these diseases remains undiscovered. In the coming years studies of complex diseases like asthma and allergy will probably involve the use of high-throughput next-generation sequencing, which will bring a tremendous influx of new information as well as new problems in dealing with vast datasets.

Keywords: genome-wide association study, high-throughput next-generation sequencing, allergy, environmental irritant, allergen

Introduction

Asthma is a chronic inflammatory condition of the lungs characterized by excessive responsiveness of the lungs to stimuli in the forms of infections, allergens, and environmental irritants.

Due to the variability of the disease and lack of generally agreed-on standards for diagnosis, it can be difficult to estimate the prevalence of asthma. Further, variations in practice from country to country complicate worldwide estimates. In the USA, it is estimated that at least 22.9 million Americans suffer from the condition. Asthma is the leading chronic illness in US children, with 6.8 million affected in 2006.[1] It is estimated that 300 million individuals suffer from asthma worldwide, with increased prevalence in both adults and children in recent decades.[2] Prevalence is rising in locations where rates were previously low and variation in rates from country to country appears to be diminishing.[3] Twin studies have shown that there is a genetic element to asthma susceptibility, with heritability of the condition estimated at between 36% and 77%.[4–7] Since the publication of the first study linking a genetic locus to asthma in 1989, more than 100 candidate genes have been reported in connection to asthma or asthma-related phenotypes such as bronchial hyperresponsiveness and elevated levels

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of serum immunoglobulin (Ig) E. Initial studies were usually candidate-gene analyses, examining the role of specific loci in asthma in a hypothesis-based manner. A few loci were identified in a hypothesis-independent manner through traditional linkage analysis. Recently, the application of genome-wide association (GWA) studies has led to the hypothesis-independent identification of a much larger list of loci associated with asthma.

Functional categories revealed through genetic analyses

Before describing the loci identified through various study designs, it would be useful to summarize the findings of the last 25 years of genetics research in asthma. The numerous genome-wide linkage, candidate gene, and GWA studies performed on asthma and asthma-related phenotypes have resulted in an increasingly large list of genes implicated in asthma susceptibility and pathogenesis. This list can be categorized into broad functional groups, from which several themes have emerged (reviewed previously[8]).

T_H2-mediated cell response

Given the appreciation of asthma as a disease of dysregulated immunity and its connection to atopy and allergic disease, it is perhaps unsurprising that genes controlling the development and regulation of the immune response have been implicated in asthma. T helper (T_H) 2 cell-mediated adaptive immune responses have been widely recognized as a crucial component of allergic disease. Pathways involved in T_H2 cell differentiation and function have been extensively studied in asthma candidate-gene association studies. Additionally, single nucleotide polymorphisms (SNPs) in many of these genes have been associated with asthma and other allergic phenotypes. Genes important for T_H1 versus T_H2 T cell polarization, such as *GATA3, TBX21, IL4, IL4RA, STAT6*, and *IL12B*, have been implicated in asthma and allergy.[9–20] The genes encoding interleukin (IL)-13 and the beta-chain of the IgE receptor FcεR1 are well-replicated contributors to asthma susceptibility.[10,12,21–24]

Inflammation

Unsurprisingly, several genes involved in inflammation have been associated with asthma. Genes for the cytokine IL-18[25] and its receptor IL18R1[26] have been implicated, as has the general mediator of inflammation tumor necrosis factor alpha.[27] Molecular mediators of inflammation have also been implicated, with the identification of leukotriene C4 synthase and other enzymes involved in the generation of leukotrienes, such as ALOX-5.[28–30]

Environmental sensing and immune detection

A second class of associated genes is involved in the detection of pathogens and allergens. These genes include pattern-recognition receptors and extracellular receptors, such as *CD14*, *toll-like receptor* (*TLR*) *2*, *TLR4*, *TLR6*, *TLR10*, and intracellular receptors, such as *nucleotide-binding oligomerization domain-containing 1* (*NOD1/CARD4*).[31–36] Additional studies have strongly associated variations in the *human leukocyte antigen (HLA) class II* genes with asthma and allergen-specific IgE responses.[21]

Airway remodeling

A variety of genes involved in mediating the response to allergic inflammation and oxidant stress on the tissue level appears to be an important contributor to asthma susceptibility. Examples include *a disintegrin and metalloproteinase domain-containing protein 33* (*ADAM33*), which is expressed in lung fibroblasts and smooth muscle cells; the *alpha-1 chain of a specific collagen* (*COL6A5*); *DPP10*, a potentially inactive serine protease; and *G protein-coupled receptor for asthma* (*GPRA*), activation of which upregulates metalloprotease expression in the lung.[37–40]

Bronchoconstriction

Acute asthma episodes involve constriction of the airways. Genes encoding proteins involved in this process have been identified as susceptibility loci for asthma. These loci include *CHRNA3/5*, which encodes a receptor for acetylcholine; *PDE4D*, which encodes a phosphodiesterase with enzymatic activity that generates molecular mediators of smooth muscle cell constriction; and *NOS1*, which encodes a nitric oxide synthase.[41–43]

Epithelial barrier function

Studies of asthma genetics have raised new interest in the body's first-line of immune defense, the epithelial barrier, in the pathogenesis of asthma. Mutations in the *filaggrin* (*FLG*) gene were initially identified in the rare single-gene disorder ichthyosis vulgaris;[44] however, loss-of-function variants were reported subsequently to be strongly associated with atopic dermatitis, eczema, and asthma, both dependent on and independent of atopic dermatitis.[45–48] Filaggrin, a protein involved in keratin aggregation, is not expressed in the bronchial mucosa,[49] which has led others to suggest that asthma susceptibility in patients with loss-of-function *FLG* variants may be due to allergic sensitization that occurs after breakdown of the epithelial barrier.[50] Several epithelial

genes with important roles in innate and adaptive immune function have also been implicated in asthma. These genes include *defensin-beta1* (*DEFB1*; an antimicrobial peptide), *uteroglobin/Clara cell 16-kD protein* (*CC16*) (an inhibitor of dendritic cell-mediated T_H2-cell differentiation), and several chemokines (*CCL-5, -11, -24*, and *-26*) involved in the recruitment of T cells and eosinophils.[51–57]

Overview of genetic analyses of asthma

Most of the published reports examining genetic contributions to asthma have been candidate-gene studies. Over 100 loci have been associated with asthma through candidate-gene studies, in which specific genes are investigated for their involvement in the phenotype based on their suspected roles or plausible hypothetical contributions to disease. The loci identified in candidate-gene studies of asthma and associated phenotypes have been extensively reviewed elsewhere.[58–60] Among the genes identified in candidate studies are various cytokines and cytokine-signaling proteins involved in T cell survival, proliferation, and differentiation; genes involved in lung function, development, and response to stimuli; receptors for detection of microbial products; genes involved in epithelial barrier function and innate immunity,[48,53] and molecules involved in responses to the environment.[59,61–63] Genes that have been extensively replicated include the *beta2 adrenergic receptor* (*ADRB2*) gene;[64–66] the cytokines, receptors, signaling proteins, and transcription factors involved in T_H1 and T_H2 differentiation of T cells, such as *IL4*, *IL4RA*, *IFNG*, *IFNGR1*, *STAT6*, *GATA3*, and *TBX21*;[9,11,14,15,17–20] and genes involved in the cellular responses that characterize atopic disease, such as *IL13* and *FCER1B*.[12,13,22–24] Many genes identified through candidate-gene studies have failed to be replicated, either because replication has never been attempted or due to failure of replication in subsequent experiments. Failure of replication is a considerable complication in the genetic analysis of asthma.[8] Genes that have been well replicated in candidate-gene studies examining asthma are summarized in Table 1.

Genome-wide linkage studies rely on families of affected and unaffected individuals and use the differentially shared regions of inherited chromosomes to track genetic markers that segregate with the disease status. Genes within disease-associated regions become candidates for further study or for positional cloning of the disease-causing variant. Linkage studies are hypothesis-independent experiments, allowing for the identification of truly novel and previously unsuspected disease-associated variants. Due to the requirement for large family cohorts, genome-wide linkage studies can be difficult and expensive to perform, and are often sufficiently powered to detect only variants with large effects. Linkage studies have identified multiple well-replicated chromosomal regions that contain genes of biological relevance to asthma and allergic disease, including the cytokine cluster on chromosome 5q (containing *IL3*, *IL5*, and *granulocyte/macrophage colony-stimulating factor* [*GMCSF*]), *FCER1B* on 11q, *interferon g* (*IFNG*) and *STAT6* on 12q, and *IL4R* (the IL-4Ra chain, also part of the IL-13R) on 16p. Linkage studies followed by positional cloning have identified a comparatively small set of novel asthma susceptibility loci, including *CYFIP2*,[67] *DPP10*,[68] *HLAG*,[69] *PHF11*,[70] *GPRA*,[39] and *ADAM33*.[37] As molecules with plausible (and potentially drug-targetable) roles in the lung pathology of asthma, *GPRA* and *ADAM33* have generated considerable interest.[39] Genes identified through genome-wide linkage analyses are summarized in Table 2.

The availability of high-density genotyping arrays and comparatively low costs of applying such technology to increasingly large patient and control cohorts have led to the development of a third kind of genetics experiment: the GWA study. Large numbers of SNPs can be screened in large numbers of individuals and assessed for association with a disease state. As with linkage analyses, GWA studies are hypothesis-independent study designs, allowing the discovery of the contributions of novel loci. Currently, more than 30 GWA studies have been published using asthma, allergy, or related phenotypes such as serum IgE levels or blood eosinophil counts as endpoints. Many of these reports do not report any loci that reach the required level of statistical significance to be considered true GWA results. However, the reports of suggestive associations are valuable, as are reports of failures to replicate previously published results. The loci identified through GWA studies that have reached high statistical significance are summarized in Table 3. This list has grown rapidly in the last few years, as the arrays available for genotyping provide more SNPs for analysis and as researchers collaborate to assemble larger and more completely controlled cohorts to add more statistical power to their analyses.

The first GWA study that focused on bronchial asthma as an endpoint was reported in 2007.[71] Markers on chromosome 17q21 were reproducibly associated with childhood-onset asthma. The findings were replicated in German and British cohorts. Independent replication of the 17q21 association has been reported in multiple populations of

Table 1 Well-replicated loci identified through candidate-gene studies

Gene	Chromosomal locus	Function
IL10	1q31-q32	Cytokine – immune regulation
CTLA4	2q33	Control/inhibition of T cell responses/immune regulation
IL13	5q31	Induces T_H2 effector functions
IL4	5q31.1	T_H2 differentiation
CD14	5q31.1	Microbe detection – recognizes pathogen associated molecular patterns
HAVCR1	5q33.2	T cell responses – hepatitis A virus receptor
LTC4S	5q35	Leukotriene synthase – inflammatory mediator
LTA	6p21.3	Inflammatory mediator
TNF	6p21.3	Inflammatory mediator
HLA-DRB1	6p21	Major histocompatibility complex class II – antigen presentation
HLA-DQB1	6p21	
HLA-DPB1	6p21	
FCER1B	11q13	Receptor for IgE – atopy
IL18	11q22.2-q22.3	Inflammation
STAT6	12q13	IL-4 and IL-13 signaling
CMA1	14q11.2	Chymase – mast cell expressed serine protease
IL4R	16p12.1-p12.2	Alpha chain of receptors for IL-4 and IL-13
FLG	1q21.3	Epithelial integrity and barrier function
SPINK5	5q32	Epithelial serine protease inhibitor
CC16	11q12.3-q13.1	Potential immunoregulatory function – epithelial expression
NOS1	12q24.2-q24.31	Nitric oxide synthase – cellular communication
CCL11	17q21.1-q21.2	Eoxtaxin-1 – eosinophil chemoattractant
CCL5	17q11.2-q12	RANTES – chemoattractant for T cells, eosinophils, basophils
GSTM1	1p13.3	Detoxification, removal of products of oxidative stress
ADRB2	5q31-q32	Smooth muscle relaxation
GPRA	7p14.3	Regulation of metalloprotease expression, neuronal effects
NAT2	8p22	Detoxification
GSTP1	11q13	Detoxification, removal of products of oxidative stress
ACE	17q23.3	Regulation of inflammation
TBXA2R	19p13.3	Platelet aggregation
TGFB1	19q13.1	Influences cell growth, differentiation, proliferation, apoptosis
ADAM33	20p13	Cell–cell and cell–matrix interactions
GSTT1	22q11.23	Detoxification, removal of products of oxidative stress

Abbreviations: IgE, immunoglobulin E; IL, interleukin; RANTES, regulated and normal T cell expressed and secreted; T_H, Thelper.

diverse ethnic backgrounds.[72–77] This locus contains the genes *ORMDL3* and *GSDMB* and variable expression of both was linked to asthma susceptibility.[71]

A case-control GWA study of North American asthmatics of European ancestry from the Childhood Asthma Management Program (CAMP) cohort has also been reported. The strongest association found was to variants of the *PDE4D* gene on chromosome 5q12, which encodes a bronchially expressed phosphodiesterase.[42] The association of *PDE4D* to asthma was not observed in individuals of African descent. In a separate study, GWA data from the CAMP cohort was investigated for replication of previously reported candidate-gene associations.[78] Thirty-nine genes were investigated with five SNP-based associations replicating to a nominal significance in the *IRAK-3*, *PHF11*, *IL10*, *ITGB3*, *ORMDL3*, and *IL4R* genes. Another GWA study on allergic asthma in children 6 years of age has recently been reported.[79] No single SNP achieved genome-wide significance, but one SNP in an intron of *PDE11A* was cited as potentially interesting. *PDE11A* encodes a phosphodiesterase related to *PDE4D*, suggesting that this family of proteins may play a broader role in asthma pathogenesis.

Table 2 Loci identified though linkage studies and positional cloning

Gene	Chromosomal locus	Reference
DPP10	2q14.1	Allen et al[68]
GPRA	7p14.3	Laitinen et al[39]
HLAG	6p21.33	Nicolae et al[69]
ADAM33	20p13	Van Eerdewegh et al[37]
PHF11	13q14.3	Zhang et al[70]
CYFIP2	5q33.3	Noguchi et al[67]
IRAK3	12q14	Balaci et al[130]
COL6A5	3q21	Söderhäll et al[38]
OPN3/CHML	1qter	White et al[131]

An association was reported between several SNPs in the *transducin-like enhancer of split 4* (*TLE4*) gene on chromosome 9q and asthma in a population of 492 Mexican children with asthma, but, again, these associations did not reach genome-wide significance.[80] However, the investigators replicated these findings in an independent cohort of 177 Mexican case-parent trios. *TLE4* had not previously been linked to the pathogenesis of asthma, but does play a role in early B cell development.[81]

Association of asthma with SNPs in multiple genes was reported in a GWA study containing more than 10,000 asthmatics and 16,000 controls.[26] SNPs in several loci achieved genome-wide significance, including *IL1RL1* and *IL18R*, *HLA-DQ*, *IL33*, *SMAD3*, and *IL2RB*. The authors observed association with the previously reported *ORMDL3/GSDMB* locus on chromosome 17 only in childhood-onset asthma. Many of these genes have direct or indirect roles in T cell responses (*IL2RB*, *HLA-DQ*) and the development of T_H1 (*IL18R1*) or T_H2 (*IL33*) responses.

A GWA study from our group was recently reported on a series of pediatric asthma patients consisting of North American cases of European ancestry with persistent asthma requiring daily inhaled glucocorticoids for symptom control, and matched controls without asthma.[82] In this study, in addition to the previously reported 17q21 locus, we uncovered association to a novel asthma locus on chromosome 1q31. The locus contains *DENND1B*, a gene that is expressed by natural killer cells and dendritic cells. The association of *DENND1B* with asthma replicated in a cohort of African Americans, although the associated allele at each SNP was the alternative allele to that associated with asthma in the discovery set. Allele reversal at shared-risk loci can be attributed to differences in the underlying genomic architecture at the loci between populations of different ancestry. The *DENND1B* gene has since been replicated in Crohn's disease[83] and in primary biliary cirrhosis.[84]

A GWA study examining pediatric asthma in a Japanese discovery cohort and Japanese and Korean replication cohorts recently confirmed the role of the *HLA* locus in these populations.[85] Additionally, this study identified *TSLP* on chromosome 5, along with a gene-rich region on chromosome 12 and the *USP38-GAB1* region on chromosome 4.

Four loci were identified in a GWA study that examined Australian cases and controls in combination with large numbers of genotyped samples from the GABRIEL (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) Consortium and multiple in silico cohorts.[86] Reported statistically significant loci were *IL6R* on chromosome 1, *C11orf30/LRRC32* on chromosome 11, *PRKG1* on chromosome 10, and *RPL32P28/OR7E156P* on chromosome 13. The locus on chromosome 11 was also associated with atopy among asthmatics.

A recent meta-analysis examined three ethnically diverse North American populations (European American, African American or African Caribbean, and Latino), searching for asthma susceptibility loci that replicated across ethnic cohorts.[87] Four previously identified loci were identified in this study (17q21, *IL1RL1*, *TSLP*, *IL33*), although this is the first report that has shown they are shared across three ethnic groups. Additionally, the *PYHIN1* locus was identified as a new susceptibility locus in African Americans.

Several GWA studies have been reported using intermediate phenotypes and quantitative traits, rather than asthma itself, as study endpoints. The first report used GWAs to identify variants that modulate serum protein levels.[88] A promoter SNP in the *CHI3L1* gene that encodes the chitinase-like protein YKL-40 was shown to influence serum YKL-40 levels and to be weakly associated with asthma, bronchial responsiveness, and pulmonary function in the Hutterite population. A GWA study showed significant association of the *FCER1A* and *RAD50* genes with expression of CHI3L1, and evidence for association of the *STAT6* gene with IgE levels. IgE levels are closely correlated with the clinical expression and severity of both asthma and allergy. The *RAD50* variants were further shown to be associated with increased risk of asthma and atopic eczema.[89] Several loci (*IL4R*, *FCER1A*, *IL13*, *STAT6*, and *HLA*) with known functions in T_H2 and allergic responses were associated with IgE levels in another recent GWA study.[90]

Eosinophils are leukocytes that play an important role in the initiation and propagation of inflammatory signals. This makes them probable mediators of inflammatory disease and a GWA study was performed examining blood eosinophil counts.[91]

Table 3 Genome-wide association study loci referenced in this review

Reported gene	Locus	Top single nucleotide polymorphism	Endpoint analyzed	Reference
ORMDL3	17q12	rs7216389	Asthma	Moffatt et al[71]
CHI3L1	1q32.1	rs4950928	Asthma/YKL-40 serum levels	Ober et al[88]
IL1RL1	2q12.1	rs1420101	Asthma/blood	Gudbjartsson et al[91]
IKZF2	5q31.1	rs12619285	Eosinophil count	
GATA2	3q21.3	rs4857855		
IL5	2q12.1	rs4143832		
SH2B3	12q24.12	rs3184504		
TLE4	9q21.31	rs2378383	Asthma	Hancock et al[80]
PDE4D	5q12.1	rs1588265	Asthma	Himes et al[42]
PDE11A	2q31.2	rs11684634	Asthma	DeWan et al[79]
RAD50	5q31.1	rs2244012	Asthma	Li et al[21]
HLA-DR/DQ	6p21.32	rs3998159		
ADRA1B	5q33	rs10515807	Asthma	Mathias et al[132]
PRNP	20p12	rs6052761		
DPP10	12q12.3	rs1435879		
IL1RL1/IL18R1	2q12.1	rs3771166	Asthma	Moffatt et al[26]
HLA-DQ	6p21.32	rs9273349	Childhood-onset asthma	
IL33	9p24.1	rs1342326		
SMAD3	15q22.33	rs744910		
IL2RB	22q12.3	rs2284033		
ORMDL3/GSDMB	17q12	rs2305480		
HLA-DPA1/HLA-DPB1	6p21.3	rs987870	Pediatric asthma	Noguchi et al[133]
DENND1B	1q31.3	rs2786098	Pediatric asthma	Sleiman et al[82]
IL6R	1q21.3	rs4129267	Asthma	Ferreira et al[86]
C11orf30/LRRC32	11q13.5	rs7130588		
USP38-GAB1	4q31	rs7686660	Asthma	Hirota et al[85]
TSLP/WDR36	5q22	rs1837253		
NOTCH4/HLA-DRA/	6p21.32	rs404860		
HLA-DQA2/IKZF4	6p21.32	rs404860		
LOC338591	10p14	rs10508372		
IKZF4/CDK2	12q13	rs1701704		
GSDMB	17q12	rs11078927	Asthma in four ethnically diverse North American populations	Torgerson et al[87]
IL1RL1	2q12.1	rs10173081		
TSLP	5q22.1	rs1837253		
IL33	9p24.1	rs2381416		
PYHIN1	1q23.1	rs1102000		
C11orf71	11q23.2	rs11214966		
CRCT1	1q21.3	rs4845783		
ORMDL3	17q12	rs6503525	Asthma	Ferreira et al[77]
C11orf30/LRRC32	11q13.5	rs2155219	Allergic rhinitis/grass sensitization	Ramasamy et al[90]
TMEM232/SLC25A46	5q22.1	rs17513503		
HLA region	6p21	rs7775228		
FCER1A	1q23.2	rs2251746	IgE levels	Granada et al[134]
IL13	5q31.1	rs20541		
HLA-A	6p22.1	rs2571391		
STAT6/NAB2	12q13.3	rs1059513		
DARC	1q23.2	rs13962		
HLA-DQA2	6p21.32	rs2858331		
FCER1A	1q23.2	rs2427837	Serum IgE levels	Weidinger et al[89]
STAT6	12q13	rs12368672		
RAD50	5q31.1	rs2706347		
CHRNA3/5	15q24	rs8034191	COPD	Pillai et al[135]
FAM13A	4q22.1	rs7671167	COPD	Cho et al[136]
RAB4B/EGLN2/MIA/CYP2A6	19q13	rs7937	COPD	Cho et al[137]
HHIP	4q31.22	rs13147758	FEV_1/FVC	Wilk et al[92]

(*Continued*)

Table 3 (*Continued*)

Reported gene	Locus	Top single nucleotide polymorphism	Endpoint analyzed	Reference
HHIP	4q31.22	rs1980057	FEV_1/FVC	Hancock et al[93]
GPR126	6q24.1	rs3817928	FEV_1/FVC	
ADAM19	5q33	rs2277027	FEV_1/FVC	
AGER-PPT2	6p21.3	rs2070600	FEV_1/FVC	
FAM13A	4q22.1	rs2869967	FEV_1/FVC	
PTCH1	9q22.32	rs16909898	FEV_1/FVC	
PID1	2q36.3	rs1435867	FEV_1/FVC	
HTR4	5q33.1	rs11168048	FEV_1/FVC	
INTS12-GSTCD-NPNT	4q24	rs17331332	FEV_1	
TNS1	2q35	rs2571445	FEV_1	Repapi et al[94]
GSTCD	4q24	rs10516526	FEV_1	
HHIP	4q31.22	rs12504628	FEV_1/FVC	
HTR4	5q33.1	rs3995090	FEV_1	
AGER	6p21.32	rs2070600	FEV_1/FVC	
THSD4	15q23	rs12899618	FEV_1/FVC	
MFAP2	1p36.13	rs2284746	FEV_1/FVC	Soler Artigas et al[138]
TGFB2	1q41	rs993925	FEV_1/FVC	
HDAC4	2q37.3	rs12477314	FEV_1/FVC	
RARB	3p24	rs1529672	FEV_1/FVC	
MECOM	3q26	rs1344555	FEV_1	
SPATA9	5q15	rs153916	FEV_1/FVC	
ZKSCAN3	6p22.1	rs6903828	FEV_1	
NCR3	6p21.3	rs2857595	FEV_1/FVC	
ARMC2	6q21	rs2798641	FEV_1/FVC	
C10orf11	10q22.2	rs11001819	FEV_1	
LRP1	12q13.3	rs11172113	FEV_1/FVC	
CCDC38	12q23.1	rs1036429	FEV_1/FVC	
MMP15	16q21	rs12447804	FEV_1/FVC	
CFDP1	16q23.1	rs2865531	FEV_1/FVC	
KCNE2	21q22.1	rs9978142	FEV_1/FVC	
DLEU7	13q14.3	rs9316500	FEV_1	Imboden et al[139]

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.

Five loci reached GWA significance, one of which, *IL1RL1*, was also shown to be associated with asthma in a collection of ten different populations.

Altered lung function, and airflow obstruction in particular, is associated with both asthma and chronic obstructive pulmonary disease. Two SNPs at the α-nicotinic acetylcholine receptor (*CHRNA3/5*) surpassed genome-wide significance in the study and replicated in two of three independent cohorts. The authors also reported that SNPs at the *HHIP* locus on chromosome 4 showed association and were consistently replicated across the study cohorts but did not reach genome-wide significance.[41] In the first of the three lung-function GWA studies that included 7691 Framingham Heart Study participants, the only locus to surpass genome-wide significance for association with forced expiratory volume in 1 second/forced vital capacity ratio and replicate in an independent cohort of 835 Family Heart Study participants was *HHIP*.[92] Two studies resulted in the identification of eleven novel loci associated with measures of lung function; both studies also replicated the previously reported association of the *HHIP* locus.[93,94]

The future of asthma genetics

New technology

As the technologies that exist for the identification of genetic variants and the analysis of those variants continue to evolve, the information dealing with the effects of genetic variations on the development of and susceptibility to asthma will grow at a rapidly increasing pace. The advent of next-generation sequencing is bringing complete sequences of genomes and exomes into the public domain. High-throughput sequencing will allow the identification of rare variants with minor allele frequencies far too low to be captured with array technologies that contribute to complex common diseases like asthma. An excellent recent report used targeted sequencing of nine candidate genes to discover rare variants in those loci that

associate with asthma.[95] The authors show evidence for the probable existence of rare variants that associate with asthma and identify variants in the *IL12RB1* locus that contribute to asthma susceptibility in Americans of both European and African ancestries. Many of the associated variants were unexpectedly found in noncoding regions of these genes, indicating that regulation of the genes plays a crucial role in disease susceptibility. Future efforts that include whole exome and whole genome sequencing will greatly expand this type of information, while bringing the considerable challenge of identifying which variants in an individual are relevant for the diseases being studied.

An additional factor to consider is the issue of uncharacterized genes. Many of the most recent GWA studies have identified loci associated with asthma containing genes that have either no known function or no known function that is easily correlated with the disease phenotype. Genes involved in the development of the immune system or specifically in the skewing of the immune response towards or away from an allergic phenotype have obvious implications for asthma susceptibility or severity. However, genes are now being identified with no obvious connections to asthma. The *DENND1B*[82] and *ORMDL3*[26] loci are examples of genes that are difficult to connect to asthma-related phenotypes. Additionally, the list of loci in Table 3 includes several loci corresponding to completely uncharacterized genes with no known function *(c11orf30/LRRC32)*,[86,90] *(c11orf71)*,[87] *(GPR126)*,[93] *(c10or11)*,[138] or to pseudogenes *(LOC338591)*[85] reported to be unexpressed. A sizeable effort will be required to understand how these genes contribute to asthma and it remains to be seen if researchers will undertake such challenges and if institutes and agencies will provide funding for this kind of work.

Gene–environment interactions

Asthma, as an immune-mediated disease, involves the response of the body to the environment, in the form of pollutants, allergens, viruses, and other pathogens and irritants. These environmental factors interact with genetic variation to influence the development or severity of disease. Researchers are finding that specific genetic variants affect susceptibility to, and the severity of, asthma in different ways depending on the environments of the individuals carrying those variants, a phenomenon known as "gene–environment interaction." Several examples of gene–environment interaction exist in asthma, with perhaps the best characterized being *CD14*, which was originally associated with asthma in linkage studies.[96–100] A polymorphism in the *CD14* promoter was associated with increased CD14 protein levels in serum and reduced serum IgE levels.[101,102] Several studies attempted to associate this polymorphism with asthma, with conflicting results.[103–109] These conflicts were resolved when the polymorphism was considered in the context of environmental influences. Different alleles of the CD14 promoter were associated with allergic phenotypes in children, depending on the type of pets or animals to which the children were exposed. One allele correlated with higher IgE levels in children exposed to household pets such as cats and dogs, while the other allele associated with the same phenotype in children exposed to stable animals like horses.[110] Homozygotes for one allele were found to be at lower risk for asthma if exposed to comparatively low levels of house dust endotoxin but at higher risk at higher endotoxin exposures.[111] Other polymorphisms at the *CD14* locus have been associated with different outcomes in specific populations, depending on environmental exposure.[105] Given the large number of identified asthma susceptibility loci and the daunting number of environmental variables that may influence complex diseases, much work remains to be done before we have a reasonable understanding of the roles of gene–environment interactions in asthma.

Gene–gene interactions

A comparatively small number of studies have been published to date examining the role in asthma of gene–gene interactions, where variation at one locus alters the effects of variations at a second locus, reflecting epitasis between two or more genes. The existing literature consists mainly of studies in which researchers have chosen two or more specific genes (and occasionally specific variants of those genes) to examine in the context of asthma, looking for evidence of interactions between the two loci. Examples of gene–gene interactions that have been observed in association with asthma include *IL9* and *IL9R* polymorphisms in Koreans,[112] *TGFBR2* and *FOXP3* in specific IgE production,[113] *IL13* and *IL4* in Dutch cohorts,[114] and *LTA4H* and *ALOX5 AP* in Latinos.[30] Larger scale analysis examining 169 SNPs in 29 genes identified a number of gene–gene interactions affecting both total and antigen-specific IgE levels.[115] Methods are actively being developed to enable large scale and unbiased analysis of gene–gene interactions[116] and visualization of the resulting networks,[117] but these efforts are in their relative infancy. Given the number of previously identified relevant genes and the possibilities for discovery of new loci, the combinatorial potential for interactions between gene effects is daunting. Much development of methods and tools remains to be done before we can truly grasp these vast possibilities.

Pharmacogenetics

Pharmacogenetics, in which variations in genotype are examined for their effects on the response to treatments, is of growing interest with asthma, with the hope that it will increase efficacy and reduce toxic side effects of medications. The best example at this time is provided by beta-adrenergic receptor agonists (or simply beta-agonists), which are prescribed to treat bronchoconstriction and provide long-term symptom control for asthmatics. The *ARDB2* locus encodes the $beta_2$-adrenergic receptor, which binds to and is activated by beta-agonists. Two studies have implicated variations in *ARDB2* as modulators of response to inhaled bronchodilators.[118,119] However, a randomized double-blind study was performed in which subjects were genotyped before being enrolled so that they could be stratified by genotype before receiving prescriptions.[120] This study showed no association of genotype with the response to beta-agonists. Another study showed that a polymorphism in the ARDB2 protein influences the response to regularly administered albuterol, with one genotype receiving less relief from regular long-term use of short-acting beta-agonists.[121] Yet another group has shown that genotype at *ARDB2* does not affect the response to combined beta-agonist and inhaled corticosteroid treatment.[122]

A recent study identified variants in the promoter of the *GLCCI1* gene that are associated with reduced responses to inhaled glucocorticoids.[123] A specific promoter variant was found to possess reduced transcriptional activity in reporter assays. The same variant was associated with reduced changes in lung function following glucocorticoid treatment. The authors calculate that this variant accounts for about 6.6% of the variability in inhaled glucocorticoid responses. Another recent publication reports variants in the low affinity IgE receptor gene, *FCER2*, associated with severe exacerbations in children in a trial of inhaled glucocorticoids. The association was present in both European Americans and African Americans and one of the polymorphisms correlated with reduced FCER2 expression. Variants have been identified that alter the response to a 5-lipoxygenase inhibitor[124] and that associate with variability in the response to a cysteinyl leukotriene receptor 1 antagonist.[125] Polymorphisms in corticotrophin-releasing hormone receptor (*CRHR1*)[126] and the *STIP1* gene (involved in the signaling initiated by glucocorticoids)[127] associate with variable forced expiratory volume in 1 second response after inhaled glucocorticoid treatment, as do polymorphisms in *TBX21*, encoding a transcription factor important in the generation of T_H1 cells.[19] This latter study demonstrates that variations in genes not directly involved in the metabolism or signaling cascades of a drug can be important modulators of the response to that drug. New study designs and analysis techniques will be required if the pharmacogenetics field is to be able to account for all the variables that may contribute to variable responses to therapies.

Conclusion

Considerable challenges remain in our understanding of the genetic underpinnings of asthma. The incredibly large quantity of data collected to date only explains a fraction of the heritability of asthma. This missing heritability is a common problem in the genetics of complex diseases. Future GWA studies may fill some of the gap in knowledge, although GWA studies are best suited to finding relatively common alleles of modest effect sizes. The use of next-generation sequencing in complex disease research may bring the identification of rare variants with larger effects, which will likely explain at least some of the missing heritability. Additionally, techniques for studying epigenetic phenomena, such as DNA methylation, have the power to expand our understanding of the causes of asthma. Recently, variations in DNA methylation in transformed B cells were described at a specific locus in a specific subset of asthmatics.[128] Variations, including methylation, in the promoter of the *Prostaglandin D2 receptor* gene, were reported in cohorts of asthmatic and atopic individuals.[129] It is probable that many more epigenetic variations, in a variety of cell types relevant to the development, severity, and treatment of asthma, will be reported in the near future. The expanded genetic and epigenetic information from future studies, combined with improved understanding and analysis of gene–gene and gene–environment interactions are likely to fill many of the gaps in our current understanding and allow us to improve the care we provide to asthma sufferers.

Disclosure

The authors declare no conflicts of interest in this work.

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