

# Present status on the genetic studies of asthma

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Asthma, one of the most common chronic diseases, is a complex and heterogeneous disorder. The results of genome screens for asthma-related traits in 11 different populations identified at least 18 regions of the genome that probably house asthma/atopy genes. The most consistently replicated regions are on chromosomes 2q, 5q, 6p, 12q and 13q. Positional cloning projects are ongoing in laboratories around the world to identify the asthma susceptibility loci in these regions. In addition, many candidate genes have been associated with asthma phenotypes, such as the genes in the IL-4/IL-13 pathway.

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### Abbreviations

<b>AD</b>	atopic dermatitis
<b>ADAM</b>	a disintegrin and metalloproteinase domain
<b>BHR</b>	bronchial hyperresponsiveness
<b>CNS</b>	conserved non-coding sequence
<b>CSGA</b>	Collaborative Study on the Genetics of Asthma
<b>IL</b>	interleukin
<b>SNP</b>	single nucleotide polymorphism
<b>SPT</b>	skin-prick test
<b>STAT6</b>	signal transducer and activator of transcription 6
<b>Th</b>	T helper
<b>UTR</b>	untranslated region
<b>YAC</b>	yeast artificial chromosome

### Introduction

Asthma affects nearly 155 million individuals worldwide [1,2]. The rising incidence of asthma over the past decades suggests that environmental and lifestyle factors are important [3]. Nonetheless, asthma clusters in families and twin studies suggest a strong genetic component to both asthma and atopy [4]. Yet, identifying asthma genes has been a daunting task. Table 1 lists some of the features that make the genetic dissection of complex disorders so challenging. To date, genome-wide screens for asthma/atopy susceptibility loci have been completed in 11 populations, with overlapping as well as discordant results. This article presents an overview of the current status of asthma and atopy genome-wide studies, along with a review of the genetics of the IL-4/IL-13 pathway.

### Genome-wide screens

One approach for mapping asthma genes is the genome-wide screen. With this approach, genetic markers throughout the genome are genotyped in family members, and used to identify chromosomal regions that are co-inherited (or

'linked') with a particular phenotype, such as asthma, bronchial hyperresponsiveness (BHR) or a positive skin-prick test (SPT). In contrast to candidate gene studies (see below), this approach could identify all genes with detectable effects on asthma susceptibility, regardless of any prior knowledge of the function of the susceptibility locus. Following fine mapping in linked regions, positional cloning or positional candidate cloning is performed to identify variation in a particular gene (or genes) that is associated with susceptibility.

Genome screens for asthma and related phenotypes have been completed in 11 study populations (Table 2; [5,6,7–17]). Details of these genome screens are available in the Asthma Gene Database [18]. Overall the results vary substantially, which could be due to differences in study design and sample size, as well as the fact that asthma is a heterogeneous disease. Nevertheless, using recommended criteria [19], 18 regions had P values that met the criteria for suggestive evidence of linkage ( $P \leq 0.002$  or  $\text{LOD} \geq 1.9$ ) in at least two studies or genome-wide significance ( $P \leq 0.000049$  or  $\text{LOD} \geq 3.3$ ) in at least one study (Table 3). Among the five regions meeting genome-wide criteria (2p, 2q, 5q, 7q and 11q), regions on 5q and 2q also show suggestive evidence for linkage in two or more additional studies. Thus, these two regions probably contain true susceptibility loci. Furthermore, markers on 13q showed suggestive evidence for linkage to asthma-related phenotypes in five studies. For two other regions, 6p and 12q, suggestive evidence for linkage was reported in four studies. Interestingly, the syntenic regions to 5q, 6p and 12q regions are also linked to BHR phenotypes in mouse models [20–23], and additional linkages and associations with genes or markers in these regions have been reported in many human populations (below and reviewed in [24,25–27]).

Overall, results of the genome screens provide compelling evidence for at least 18 genes contributing significantly to asthma/atopy, which reflects the extensive heterogeneity that characterizes these phenotypes. The fact that some regions are relatively broad further suggests that there may be more than one susceptibility locus in each region. Additionally, markers in most regions are linked to a variety of asthma-related phenotypes, reflecting the considerable overlap in loci that contribute to asthma and atopic phenotypes. Yet, despite these complexities, positional cloning projects are ongoing in laboratories around the world and asthma genes will probably be identified in the near future, although each locus will probably contribute little to overall asthma risk (see Update). It is possible, and even likely, that these studies will identify novel pathways involved in asthma pathogenesis, which could facilitate the identification of additional susceptibility loci and the development of new therapeutic targets.

**Table 1****Characteristics of common complex diseases that affect genetic studies.**

Characteristic	Implication for genetic studies
Multifactorial Heterogeneous	Causes include genetic and environmental factors More than one gene contributing to susceptibility Susceptibility in different families may be caused by different genes
Reduced penetrance Presence of phenocopies	Unaffected individuals may carry the susceptible genotype Individuals in one family may have the same phenotype for different underlying causes, either genetic or environmental
Variable expression of phenotypes	Individuals with the same genetic susceptibility may have different expressions of disease, with respect to age of onset, disease severity and associated phenotypes
Gene–gene interactions	Several susceptibility genes may interact in a complex fashion (e.g. see [6',69'])
Gene–environment interactions	Environmental factors may trigger disease expression in genetically susceptible individuals (e.g. see [79,80])

**Candidate gene studies**

A second, more focused, approach is to study variation in candidate genes. In this approach, known genes ('candidates') are chosen because their function implicates them in asthma pathophysiology. Using case control study designs, associations between one or more polymorphisms in the candidate gene and an asthma/atopy phenotype are evaluated. There have been many studies of genes in the cytokine cluster on chromosome 5q (*IL4*, *IL13*, *IL9*, *IL5*, *CD14* and  $\beta_2$  adrenergic receptor [*ADRB2*]), the human leukocyte antigen (HLA) region on chromosome 6p (including the *TNF* gene), the high affinity IgE receptor (*FCERB*) and the Clara cell secretory protein (*CC16*) on chromosome 11q, and the  $\alpha$  chain of the IL-4 receptor (*IL4RA*) on chromosome 16p (reviewed in [27]). Overall, results of candidate gene studies vary enormously, and associations found in some populations are often not replicated in others. This is not completely unexpected for phenotypes as complex as asthma, but makes it difficult to determine whether they represent true associations or type I errors.

By contrast, genes involved in the IL-4/IL-13 pathway have been associated with asthma/atopy phenotypes in many studies. Because of the key role of this pathway in asthma [28], and the overall consistency of the results, these studies are described in detail below.

**Studies of genes in the interleukin-4/interleukin-13 pathway**

Both IL-4 and IL-13 are important T helper 2 (Th2) cytokines that trigger isotype switching from IgG or IgM to IgE in B cells [29]. Although IL-4 was initially considered to be the 'classical' Th2 cytokine, it is now clear that IL-13 plays an important role in asthma pathogenesis independently of IL-4 [28]. The genes encoding both cytokines lie adjacent to each other in the cytokine cluster on chromosome 5q31, which has been linked to asthma in genome screens (see above) as well as in regional linkage studies (e.g. [30–33]). Furthermore, studies in mice that are transgenic for a human yeast artificial chromosome (YAC) containing the *IL4* and *IL13* loci along with the intergenic region on

5q revealed functional effects on *IL4* and *IL13* expression, which influenced asthma-associated phenotypes *in vivo* [34]. The receptors for these cytokines share a common  $\alpha$  chain whose gene, *IL4RA*, is located on chromosome 16p12. This chain dimerizes with the common  $\gamma$  chain in the IL-4 receptor and with the IL-13  $R\alpha 1$  chain in the IL-13 receptor. Polymorphisms in both cytokine and receptor genes have been associated with asthma or associated phenotypes.

**Interleukin-4**

In 1995, Rosenwasser *et al.* [35] described a functional promoter polymorphism (–590C/T) in the *IL4* gene, which was associated with elevated IgE levels in asthmatic individuals. This polymorphism has since been associated with asthma-related traits in some studies, although most failed to confirm these associations [36–40]. Interestingly, Zhu *et al.* [41] recently reported that the –590T allele (referred to as –589T in this study) was associated with 'probable asthma' at one year of age in a prospective cohort of high-risk children, and suggested that this allele might be a predictor for the early inception of asthma; however, two other recent studies did not find association with childhood atopic asthma [39] or AD [42]. Suzuki *et al.* [43] identified another promoter single nucleotide polymorphism (SNP; +33C/T), which was associated with elevated total IgE levels in their patients. Most studies, however, do not find association with variation in the *IL4* gene, which also does not account for the evidence of linkage to the 5q cytokine cluster [8,32,44]. Overall, therefore, it is unlikely that the *IL4* gene contributes significantly to asthma susceptibility, although it may play a more significant role in allergic disease.

**Interleukin-13**

The gene encoding IL-13 resides only 25 kb upstream of the *IL4* gene. Van der Pouw Kraan *et al.* [45] first described a C/T polymorphism at nt–1111 (referred to as –1055 in this study) that was associated with allergic asthma, altered regulation of IL-13 production and increased binding of nuclear proteins. Association of this promoter SNP with BHR was reported in another Dutch population [46]. A coding SNP in exon 4

**Table 2****Genome-wide searches for susceptibility loci for asthma, atopy and associated phenotypes.**

Study	Sample	Ascertainment	Phenotypes studied
Daniels <i>et al.</i> [5]	172 sib pairs in 80 families from Busselton, Western Australia (primary sample) and 268 sib pairs in 77 families from UK (replication sample)	Population-based	Slope BHR Atopy score Skin-test index Total serum IgE Eosinophil count Asthma
CSGA [6,7]	266 families from three ethnic groups in the United States	Sib pairs with asthma	Asthma Total serum IgE
Ober <i>et al.</i> [8]	Inbred Hutterite pedigree; 693 individuals	Population-based	Asthma BHR Symptoms SPT to 14 allergens
Wjst <i>et al.</i> [9]	156 affected sib pairs from 97 German families	Sib pairs with asthma	Asthma BHR Slope BHR Peak flow Total serum IgE RAST Eosinophil count
Dizier <i>et al.</i> [10]	297 affected sib pairs in 107 French families (46 families in the primary sample, 61 in the replication sample)	Sib pairs with asthma	Asthma SPT Slope BHR Total serum IgE Eosinophil count
Xu <i>et al.</i> [11]/ Koppelman <i>et al.</i> [12]	1174 individuals in 200 Dutch families	Parent with asthma diagnosed between 1962 and 1975	Total serum IgE Specific IgE to aeroallergens SPT to 16 allergens Eosinophil count
Yokouchi <i>et al.</i> [13]	65 affected sib pairs in 47 Japanese families (Japanese 1)	Sib pairs with mite-sensitive atopic asthma	Mite-sensitive atopic asthma
Laitinen <i>et al.</i> [16]	220 affected individuals (asthma) in 86 Finnish pedigrees (primary sample); 80 affected individuals (asthma) in 22 French-Canadian families (replication 1) and 114 affected individuals (high IgE) in 29 families (replication 2)	Relative pairs with asthma (primary sample, replication 1) or high IgE (replication 2)	Asthma
Xu <i>et al.</i> [15]	2551 individuals in 533 Chinese families	Sib pairs with asthma	FEV <sub>1</sub> , FVC Slope BHR Total serum IgE Eosinophil count SPT to cockroach and HDM
Haagerup <i>et al.</i> [17]	33 affected sib pairs in 33 Danish families	Sib pairs with allergic rhinitis	Allergic rhinitis
Yokouchi <i>et al.</i> [14]	67 affected sib pairs in 48 Japanese families (Japanese 2)	Sib pairs with orchard grass-sensitive seasonal allergic rhinitis	Seasonal allergic rhinitis Orchard grass-specific RAST Total serum IgE

FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; HDM, house dust mite; RAST, radio allegro sorbent test; Sib, sibling.

(G4464A) that results in an amino acid exchange from arginine to glutamine at position 110 (Arg110Gln) was identified and shown to influence serum IL-13 levels [47\*]. Furthermore, molecular modeling indicated that this site is important for ligand–receptor interaction [47\*]. This variant was subsequently associated with elevated IgE in 1399 children from three populations [48]; with asthma in British and Japanese populations [47\*]; with elevated IgE and AD in a German multicenter allergy study [49]; and with elevated total and specific IgE (but not asthma) in Hong Kong

Chinese children [50]; however, studies in a large Hutterite pedigree [8] and in 83 Costa Rican families [51] failed to replicate association of the Arg110Gln locus with asthma phenotypes. Nevertheless, the association of variants in *IL13* with asthma-related traits in diverse populations suggests that the *IL13* gene is indeed an asthma susceptibility locus. The differences between studies with respect to the associated polymorphisms and phenotypes, as well as the magnitude of the effect, may reflect differences in background genes or environmental exposures (reviewed in [52]).

**Table 3****Regions showing a P value  $\leq 0.000049$  or a LOD  $\geq 3.3$  in at least one study or  $P \leq 0.002/\text{LOD} \geq 1.9$  in at least two studies.**

Chromosome	cM from pter*	Study population†	Phenotypes	Linkage to syntenic region in mouse models
1p	4	Hutterites	Strict asthma (P=0.0002)	
2p‡	~10	Japanese 2	SAR, total IgE (P<0.002)	
2q‡	173–210	Chinese	Slope BHR (P=0.00002)	
		Hutterites	SPT cockroach (P=0.00004)	
		German	Total IgE (P=0.0016)	
		Dutch	Total IgE (LOD=1.96), eosinophils (LOD=1.49)	
3p	52–68	Hutterites	Loose asthma (P=0.0004)	
		Japanese 2	Total IgE (P<0.001)	
4q	104–117	Chinese	SPT (P=0.0003)	
		Danish	Allergic rhinitis (LOD=2.83)	
4q	181–207	Japanese 1	Mite-sensitive asthma (P=0.0002)	
		Busselton	Slope BHR (P<0.0005)	
5p	33–45	French	Slope BHR (P=0.001)	
		Hutterites	BHR (P=0.001)	
5q‡	130–172	Japanese 1	Mite-sensitive asthma (P=0.0000013)	BALBc×BP <sub>1</sub> F <sub>2</sub> : eosinophil
		Hutterites	Asthma symptoms (P=0.0009)	Infiltration in bronchial
		Dutch	Total IgE (LOD=2.73)	epithelium (LOD=2.5) [23]
		Japanese 2	Total IgE (P<0.001)	
6p	34–60	Busselton	Eosinophils (P<0.0001), atopy (P<0.005), total IgE (P<0.05)	BALBc×BP <sub>1</sub> F <sub>2</sub> : BHR (LOD=2.1) [23], (AJ×C3H/HeJ)F <sub>1</sub> ×C3H/HeJ: BHR (LOD=1.7) [21], C57BL/6J×A/J) F <sub>1</sub> ×C57BL/6J: BHR (LOD=2.83) [20]
		CSGA (Caucasians)	Asthma (P=0.003, LOD=1.91)	
		German	Total IgE (P=0.0012), RAST (P=0.0011), Eosinophils (P=0.0005), asthma (P=0.0081)	
		Japanese 1	Mite-sensitive asthma (P=0.0009)	
7p	50–67	Busselton	BHR (P<0.0005), total IgE (P<0.005), Eosinophils (P<0.05)	
		Finnish	IgE, asthma (lowest P=0.0001)	
		French	Eosinophils (P=0.002)	
7q‡	98–109	Dutch	Total IgE (LOD=3.36), SPT aeroallergens (LOD=1.04)	
11q‡	58–60	Busselton	Skin test index (P<0.00005), total IgE (P<0.005)	
		CSGA (African American)	Asthma (LOD=2.00)	
12q	111–134	French	Eosinophils (P=0.0003)	BALBc×BP <sub>1</sub> F <sub>2</sub> : BHR (LOD=3.8) [23]
		Japanese 1	Mite-sensitive asthma (P=0.001)	
		Dutch	Total IgE (LOD=2.46, P=0.0004)	
		Japanese 2	Total IgE (P<0.001)	
13q	6–45	Hutterites	Asthma symptoms (P=0.0006)	
		Japanese 1	Mite-sensitive asthma (P=0.0004, P=0.001)	
		Dutch	Total IgE (LOD=2.28), SPT (LOD=1.27)	
		Busselton	Atopy (P<0.001)	
		French	Eosinophils (P=0.002)	
16p	40–42	Chinese	FVC (P=0.0006)	
		Japanese 2	RAST orchard grass (P<0.001)	
16q	105–125	Busselton	Total IgE (P<0.0005), slope BHR (P<0.05)	
		Hutterites	SPT molds (P=0.0008)	
17q	62–100	French	SPT (P=0.001), asthma (P=0.003)	BALBc×BP <sub>1</sub> F <sub>2</sub> : BHR (LOD=3.8) [23]
		Dutch	Eosinophils (LOD=1.97), SPT mite (LOD=1.21)	
19q	52–70	Hutterites	BHR (P<0.001)	(AJ×C3H/HeJ)F <sub>1</sub> ×A/J: Allergen-induced BHR (LOD=1.9) [22], (AJ×C3H/HeJ)F <sub>1</sub> ×C3H/HeJ: BHR (LOD=3.8) [21]
		Chinese	BHR (P=0.002)	

Regions were identified by markers showing evidence for linkages that were  $\leq 20$  cM apart. \*Genetic (cM) distance based on the Marshfield map (<http://research.marshfieldclinic.org/genetics/>); †See Table 1 for references; ‡Regions showing genome-wide significant evidence for linkage; FVC, forced vital capacity; RAST, radio allergo sorbent test; SAR, seasonal rhinitis.

### Conserved non-coding sequence 1

Recently, studies in YAC transgenic mice revealed that a conserved non-coding sequence (CNS) between the *IL4*

and *IL13* loci (called *CNS-1*) coordinately regulates the expression of *IL4*, *IL13* and *IL5* [53\*\*]. Deletion of *cns-1* in mice compromised the capacity to develop Th2 cells,

whereas mast cells from *cns-1<sup>-/-</sup>* mice maintained their capacity to produce IL-4, suggesting a T cell-specific element critical for the optimal expression of Th2 cytokines [54]. Noguchi *et al.* [55] screened the region between *IL4* and *IL13* for polymorphisms. They did not find variation within the *CNS-1*, but identified four SNPs in the surrounding intergenic region. Haplotypes composed of *IL4* 5'-untranslated region (UTR) polymorphisms and these intergenic SNPs were significantly overtransmitted to asthmatic children, further implicating this region in asthma susceptibility. Because no variation was identified in *CNS-1* itself, it is unlikely that *CNS-1* contributes to individual differences in asthma susceptibility; however, additional studies are needed to fully assess the role of this regulatory region in asthma susceptibility.

#### Interleukin-4 receptor $\alpha$ chain

The gene encoding the  $\alpha$  chain of the IL-4 and IL-13 receptors on chromosome 16p12 has been extensively studied as an asthma candidate gene. To date, 14 SNPs in coding regions have been described [56,57,58\*,59], 10 of which result in amino acid substitutions. Three of these variants are known to be associated with functional changes in the receptor. Functional assays of Ile50Val, the only variant in the extracellular domain, suggested that Ile50 augments signal transducer and activator of transcription 6 (STAT6) activation, transcriptional activity and CD23 expression [60,61]. This variant was associated with atopic asthma in Japanese populations [39,60,61], although other studies could not replicate this association [6\*,62–64]. Functional studies on Gln551Arg in the intracellular domain have shown conflicting results. Hershey *et al.* [57] first described enhanced signaling and a change in binding specificity for the Arg551 allele, but Wang *et al.* [65] did not find this effect. Furthermore, Hershey *et al.* [62] reported an association between the Arg551 allele and hyper-IgE syndrome and severe atopic AD in a small case-control study, but so far only one group could confirm association of the Arg551 allele to AD. Others failed to replicate the association with either hyper-IgE syndrome [66] or asthma/atopy [38,63,64,67]. Kruse *et al.* [68], however, reported that both the Pro478 allele and the Arg551 allele are associated with low IgE levels in a German population, suggesting a protective role for the Arg551 allele, and that these two variants act synergistically to influence signal transduction. Consistent with the Kruse study, associations with the Ser478 and/or the Gln551 allele and asthma or atopy phenotypes have since been reported in many studies [58\*,69\*].

Because of the discordant results of association studies of the *IL4RA* gene, and the relatively large number of polymorphisms in this gene, subsequent studies have tried to address these complexities. Ober *et al.* [58\*] genotyped members of a large Hutterite pedigree for all amino acid polymorphisms in the gene. Although no individual allele was very significantly associated with asthma, haplotypes comprised of combinations of alleles in the intracellular

domain were highly associated with asthma. Similarly, in the outbred Collaborative Study on the Genetics of Asthma (CSGA) families, these haplotypes showed association with both asthma and SPT. The fact that different variants and haplotypes were associated with asthma and atopy in different populations led the authors to conclude that variation outside of the coding region might contribute to disease susceptibility. Subsequently, Hackstein *et al.* [70] identified three polymorphisms in the 5'-flanking and promoter region of *IL4RA*. Studies in healthy blood donors revealed a highly significant association of the -3223C/T polymorphism and peripheral levels of soluble IL-4R: an isoform that may play a role in either enhancing or inhibiting IL-4 signaling [71]. Because soluble IL-4R has recently been introduced into clinical therapy [72], understanding how the -3223C/T variant influences peripheral levels of this isoform may have important pharmacogenetic implications; however, functional studies are needed to investigate the underlying molecular mechanism, and studies of the -3223C/T variant in patient populations are necessary to determine whether this polymorphism influences asthma risk. Taken together, the associations between coding region variation and asthma or atopic phenotypes in at least nine independent studies suggest that the *IL4RA* gene is also an asthma susceptibility locus.

#### Gene-gene interactions in the interleukin-4/interleukin-13 pathway

Howard *et al.* [46] examined interaction effects between the *IL4RA* and *IL13* genes. Previously they reported a significant association between the *IL13* -1111C/T promoter SNP and BHR and between the *IL4RA* Ser478Pro variant and serum IgE levels [69\*]; however, when they examined the interaction effects of these two susceptibility SNPs in the same case control sample they found a significant gene-gene interaction between them: individuals who were homozygous for the *IL4RA* Ser478 allele and carried the *IL13*-1111T allele had a nearly five times greater risk of developing asthma than individuals with other genotypes [69\*]. Thus, whereas the *IL13* locus was most significantly associated with BHR and the *IL4RA* locus with IgE in this population, the combined effects of these two susceptibility loci conferred risk for asthma. This finding highlights the importance of studying gene-gene interactions in complex biological pathways, and further implicates the *IL13* and *IL4RA* genes as asthma susceptibility loci.

#### Interleukin-13 receptor $\alpha 1$ chain

Relative to *IL4RA*, there have been few genetic studies of the *IL13R* gene, which encodes the  $\alpha$  chain of the IL-13 receptor (*IL13RA1*) and is located on chromosome Xq13. Heinzmann *et al.* [47\*] identified a common polymorphism in this gene (A1398G) that showed a marginal association with high IgE levels but not asthma in a British but not a Japanese population. Another variant in *IL13RA1* (C1050T) did not show association to atopic asthma in a second

Japanese population [73]. Further studies are needed to elucidate the role of the *IL13R* genes in asthma pathobiology and to investigate possible interactions with variation in the *IL13* and *IL4RA* genes.

### Signal transducer and activator of transcription 6

STAT6 plays an important role in IL-4/IL-13 signaling; STAT6 deficient mice lack IgE production and Th2 inflammatory reactions [74,75]. Variants in the *STAT6* gene, on chromosome 12q, have been associated with asthma-related phenotypes in three studies. A SNP in the 3'UTR (G2964A) was associated with mild atopic asthma in a Japanese but not a British population [76], and a repeat polymorphism in exon 1 showed association with allergic diseases in Japanese children [77]. Recently, Duetsch *et al.* [78\*] screened the coding and promoter region of *STAT6* and identified 13 non-coding SNPs. None of the polymorphisms were associated with asthma, but a significant association was found between a SNP in intron 18 and increased total IgE levels, and between the dinucleotide repeat in exon 1 and elevated eosinophil levels. These combined data implicate the *STAT6* gene as a potential atopy susceptibility locus and warrant further investigation in additional samples.

### Conclusions

Asthma is indeed a complex phenotype with evidence that many genes as well as gene–gene interactions contribute to susceptibility. The results of genome screens for asthma-related traits in 11 different populations identified at least 18 genomic regions that probably house asthma/atopy genes. The most consistently replicated regions are on chromosomes 5q, 2q, 13q, 6p and 12q. All of these regions include interesting candidate genes that are currently being investigated in laboratories around the world. Genes in the IL-4/IL-13 pathway are particularly intriguing because of the many functions of these cytokines in asthma pathobiology. In addition, variation in genes encoding both cytokines and their intergenic region, the shared receptor  $\alpha$  chain, and the main signal transducing molecule have been associated with asthma-related traits. Evidence for gene–gene interactions between ligand and receptor further attest to the complex nature of the genetic influences on susceptibility. More sophisticated analytical approaches that identify both gene–gene and gene–environment interactions on a genome-wide level are required to fully elucidate the genetic risk factors for asthma and atopy, and to understand the pathogenesis of these common diseases.

### Update

The first asthma-susceptibility locus to be identified by positional cloning was recently reported by Van Eerdewegh *et al.* [81\*\*]. A genome-wide screen in 460 affected sibling-pair families from the UK and US revealed evidence for linkage to asthma on chromosome 20p13 (LOD = 2.94). Subsequent analysis in a subset of 218 families with asthma and BHR increased the LOD to 3.93 and narrowed

the linked region to 4.28 cM, corresponding to 2.5 Mb and containing 40 genes. 135 polymorphisms in 23 candidate genes were genotyped in 130 unrelated cases (selected from the families) and 217 non-asthmatic, matched controls. Linkage disequilibrium studies identified multiple polymorphisms in the *ADAM33* gene that were associated with asthma ( $P = 0.03$ – $0.003$ ), and haplotypes comprised of polymorphisms within *ADAM33* were significantly associated with asthma in the case-control samples, as well as in family-based association tests ( $P = 0.0004$ – $0.000003$ ). Most of the associated polymorphisms were common variants located in introns and the 3'UTR, but a few were amino acid exchanges. ADAM (a disintegrin and metalloproteinase domain) proteins are cell-surface proteins that mediate adhesion and proteolysis. *ADAM33* is expressed in bronchial smooth muscle and epithelial cells and was proposed to play a role in the remodeling process of the airways [81\*\*]. It is noteworthy that this region on 20p showed only modest evidence of linkage in other studies (e.g. [6\*]) and did not meet the criteria used to discover regions of interest in this or previous reviews [27], although it does correspond to a syntenic region in the mouse that was linked to BHR [20]. Furthermore, the associated variants in *ADAM33* are common (frequencies 0.20–0.95), and different haplotypes showed association in the different study populations. Therefore, it is likely that the *ADAM33* locus confers minor risk to asthma in the general population, not unlike other common disease genes identified through positional cloning [82].

In addition, a genome-wide screen for asthma in the Icelandic population was recently reported [83]. Markers on chromosome 14q24 showed evidence for linkage (LOD = 2.66) to asthma; the addition of markers in this region increased the LOD to 4.00 at 90 cM from pter, reaching genome-wide significance. Thus, this additional region probably houses an asthma gene in the Icelandic population and further reflects both the extensive genetic heterogeneity underlying asthma and the potential importance of environmental factors on the role of different genes in asthma pathogenesis.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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