**Review**

**Interactions between genes and environmental factors in asthma and atopy: new developments**

Claudia Sengler, Susanne Lau, Ulrich Wahn and Renate Nickel

Department of Pediatric Pneumology and Immunology, Charité, Humboldt University Berlin, Berlin, Germany

**Correspondence:** Renate Nickel, Department of Pediatric Pneumology and Immunology, Charité, Humboldt University, Augustenburger Platz 1, D-13353 Berlin, Germany. Tel: +49 30 4505 66131; fax: +49 30 4505 66931; e-mail: renate.nickel@charite.de

Received: 10 April 2001
Revisions requested: 7 June 2001
Revisions received: 10 July 2001
Accepted: 27 July 2001
Published: 31 October 2001

**Abstract**

Asthma and associated phenotypes are complex traits most probably caused by an interaction of multiple disease susceptibility genes and environmental factors. Major achievements have occurred in identifying chromosomal regions and polymorphisms in candidate genes linked to or associated with asthma, atopic dermatitis, IgE levels and response to asthma therapy. The aims of this review are to explain the methodology of genetic studies of multifactorial diseases, to summarize chromosomal regions and polymorphisms in candidate genes linked to or associated with asthma and associated traits, to list genetic alterations that may alter response to asthma therapy, and to outline genetic factors that may render individuals more susceptible to asthma and atopy due to environmental changes.

**Keywords:** asthma, atopy, environment, genetics, infection

**Introduction**

The prevalence of asthma, allergic rhinitis and atopic dermatitis (AD) has dramatically increased over the past decades. These atopy-related diseases are the most common chronic disorders in childhood in Western societies. Several epidemiological studies have evaluated environmental risk factors that may explain the steady increase of allergic disease. (Note: in this article, allergic diseases/atopic disorders include asthma, allergic rhinitis and AD. Atopy-associated phenotypes/traits include, in addition, allergic sensitization, elevated total serum IgE and eosinophilia.) There is growing evidence that contact to bacterial antigens (such as endotoxin) and viral infections in early childhood is protective with regard to development of allergic disease in later life [1–6]. Although changes in lifestyle significantly contribute to disease expression, heritability has been shown to play a major role in the pathogenesis of allergic disease.

Multiple twin and family analyses strongly imply a genetic basis for atopy-related traits (for a review, see [7]). A recent study of 11,688 Danish twin pairs (comparing identical and non-identical twin pairs) suggested that 73% of asthma susceptibility is due to genetic factors [8]. However, atopy-associated phenotypes, including asthma, do not appear to follow any Mendelian inheritance pattern, which is characteristic for complex genetic (multifactorial) traits. The dissection of these traits is hampered by pheno-}

\[\beta_2\text{AR} = \text{beta-2 adrenergic receptor; AD = atopic dermatitis; IL = interleukin; 5-LO = 5-lipoxygenase; SNP = single nucleotide polymorphism; TDT = transmission disequilibrium test.}\]

Available online http://respiratory-research.com/content/3/1/7

Respir Res 2002, 3:7

© 2002 BioMed Central Ltd
(Print ISSN 1465-9921; Online ISSN 1465-993X)
Methodology in genetic studies of complex traits

Microsatellite marker analysis

The majority of studies on genetics of complex traits to date have been based on microsatellite marker (synonym, short tandem repeat polymorphisms [STRP]) analyses. These genetic markers (whose biological function is as yet unknown) typically contain a variable number of tandem repeats of dinucleotide, trinucleotide or tetranucleotide DNA sequences (e.g. the tetranucleotide [TATA]n). The high degree of polymorphism results in great variation between individuals. Short tandem repeat polymorphisms of known location are found densely spaced throughout the genome and are used for genome-wide searches as well as for the analysis of candidate gene regions.

Study designs in analyses of complex genetic traits

Most studies on the genetics of asthma are based on allele sharing methods, transmission disequilibrium test (TDT) analysis, or tests for associations. The allele sharing methods approach involves testing how often a genetic marker (or a chromosomal region) is shared by affected pedigree members. If allele sharing occurs significantly more often than expected by chance, linkage of the particular marker and disease can be assumed, indicating that the chromosomal region containing the genetic marker also contains a gene that contributes to disease expression.

The TDT approach is based on genotype analysis of affected subjects (no siblings are required) and their parents. The TDT tests whether genetic marker alleles from heterozygous parents are transmitted as frequently as expected by chance (by random, each parental allele is transmitted with a chance of 50%). Overtransmission of a particular marker allele indicates linkage of this allele with the respective ‘disease’ allele.

Association studies are usually applied once polymorphisms in candidate genes for asthma/atopy have been identified.

Linkage and candidate gene studies in asthma and atopy

Linkage studies

Results from linkage studies (genome-wide searches and candidate gene region analyses) are summarized in Supplementary Tables 1 and 2 (see also [10–13]). Multiple chromosomal regions were related to asthma and atopy. Few regions, however, have shown evidence for linkage in more than one population (Supplementary Table 2), which may be due to racial differences, to different definition of phenotypes, or (most probably) to insufficient numbers of affected sib-pairs in different study populations. The first successful attempts have been made to pool data from genetic studies of asthma and atopy in order to analyze major candidate gene regions [14,15].

Despite the high degree of inconsistent findings, it is intriguing that chromosomal regions linked to asthma have also shown evidence for linkage to other inflammatory and autoimmune diseases (such as psoriasis, inflammatory bowel disease, type I diabetes and multiple sclerosis). Becker et al. noted that susceptibility genes for various autoimmune and inflammatory diseases (including asthma) appear to cluster in 18 distinct chromosomal regions, implying common genetic elements in inflammatory disorders [16]. This speculation is further supported by two recent genome-wide searches for AD susceptibility genes. Regions linked to AD (Supplementary Table 1) have also been linked to psoriasis in other studies [17,18], suggesting that common genetic elements are involved in dermal inflammatory disorders.

Candidate gene studies

Multiple genes are involved in the allergic inflammation (shown in Supplementary Figure 1). Multiple single nucleotide polymorphisms (SNPs) in candidate genes for asthma and atopy have been identified, and they are presented in Supplementary Table 3. The (often conflicting) results have to be interpreted with caution, since multiple genotypes are commonly tested for a large number of atopy-related (sub)phenotypes (using various statistical approaches) in often considerably small sample sizes. Therefore, type 1 errors (false-positive results) are likely to occur. In addition, publication favors positive results and, therefore, many negative studies have not been published.

Functional studies

Many SNPs listed in Supplementary Table 3 have been tested for functional differences in vitro. However, when several (potentially) functional SNPs are expressed in one (regulatory region of a) gene (e.g. IL-4Rα, IL-13, beta-2 adrenergic receptor [β2AR]), they are likely to interact. The individual analysis of SNPs may therefore not reflect in vivo gene function, as a recent study on β2AR haplotypes demonstrated (see ‘β2-agonists’ subsection). (Note: a haplotype is a particular combination of alleles in a defined region of a chromosome. It is used to describe combinations of polymorphisms in a gene/chromosomal area.) In vitro differences in gene expression or function due to SNPs therefore have to be interpreted with caution when several other polymorphisms within the same gene may also alter functionality in vitro and in vivo. This notion may explain some of the controversial findings with regard to associations of individual SNPs in polymorphic genes (e.g. IL-4Rα).

The importance of haplotype analysis is further supported by the following studies. Seven SNPs in the IL-13 gene have been shown to be tightly linked [19], and therefore association studies of individual SNPs with the assumption of independent inheritance cannot easily be performed. Also, several SNPs within the IL-4Rα gene have been iden-
tified (see Supplementary Table 3). An association of two individual SNPs (S503P and Q576R) with decreased serum IgE levels was observed in a Caucasian population; however, most significant results with regard to low IgE levels were seen when both SNPs occurred together [20].

Similarly, Ober et al. performed TDT analysis for IL-4Rα SNPs and haplotypes in four populations. Again, the strongest evidence for linkage to asthma and/or atopy was observed with two-locus haplotype analysis [21].

**Gene–gene interactions**

Gene–gene interactions also have to be taken into consideration; for example, when both the genes encoding pro-inflammatory cytokines (i.e. IL-13) as well as their receptors (IL-4Rα) and/or genes involved in signal transduction (STAT6) bear polymorphisms associated with disease. The first studies have demonstrated the feasibility and importance of gene–gene interaction in atopy [22].

**Gene–environment interactions**

**Pharmacogenetics**

A marked disparity in treatment response to pharmacotherapy is observed in asthma (as well as in many other diseases). Variations in genes encoding proteins that interact with specific drugs or drug metabolism are likely to contribute to variability in treatment response. The best examined gene with regard to pharmacogenetics is the gene encoding the enzyme cytochrome p450, for which various alterations that affect the metabolism of multiple drugs have been described. Gene chips for the determination of p450 alleles are commercially available in Sweden and North America (reviewed in [23]).

Pharmacotherapy of asthma and atopy comprises β-agonists, corticosteroids, anti-histamines (H1-receptor antagonists) and leukotriene (receptor) antagonists. The following pharmacogenetic studies have been performed.

**β-agonists**

β2-agonists are the most widely used drugs in the treatment of asthma. They exert their primary effect on the β2AR of bronchial smooth muscle. The gene encoding the β2AR maps to chromosome 5q33 and is the best examined candidate gene with regard to pharmacogenetic studies in asthma. Several SNPs within the coding region and the promoter of the β2AR have been identified (summarized in [24]; see also Supplementary Table 3). Three mutations that result in amino acid changes of the mature protein (Gly16Arg, Gln27Glu, and Thr164Ile) lead to functional changes. The Gly16 variant was shown to undergo enhanced agonist-promoted downregulation in vitro. Interestingly, a strong association of the Gly16 polymorphism and nocturnal asthma could be demonstrated [25], which may explain the β2AR downregulation observed in nocturnal asthmatics but not in non-nocturnal asthmatics [26].

Conflicting results have been reported with regard to β2AR SNPs and response to β2-agonists (summarized in Supplementary Table 3). A large multicenter study demonstrated that patients homozygous for the Arg16 variant developed a decline in peak flow when using albuterol on a regular basis [27]. However, a recent haplotype analysis [24] indicated that β2AR SNPs are not independently transmitted and should presumably not be tested separately for associations with asthma or differences in drug response. Drysdale et al. demonstrated that only a limited number of β2AR haplotypes can be found in several ethnic groups, far less than theoretically possible. Furthermore, response to β2-agonists in asthmatic individuals significantly related to distinct haplotypes but not to individual SNPs. Consistent with the in vivo data, transfection of cells with the β2AR haplotype associated with a better response to β2-agonists resulted in significant greater mRNA levels and β2AR receptor density compared with the lower response haplotype [24].

**Corticosteroids**

Despite the large variability in the steroid response of asthmatic individuals, genetic variations in the glucocorticoid receptor gene have as yet to be identified in steroid-dependent asthmatics.

**Anti-histamines**

No functionally relevant polymorphism has been found in the H1-histamine receptor gene [23]. However, a functional mutation in the gene encoding the histamine-degrading enzyme N-methyltransferase has been related to asthma [28].

**Leukotriene antagonists**

Leukotrienes (LTC4, LTD4, LTE4) contribute to airway inflammation and bronchoconstriction in asthmatic individuals. 5-lipoxygenase (5-LO) (gene symbol, ALOX5; chromosome, 10q11.2) is a crucial enzyme in the synthesis of leukotrienes. The activity of 5-LO determines, at least in part, the concentration of leukotrienes in the airways. Drazen et al. [29] described frequently occurring mutations in the 5-LO promoter (three to six tandem repeats of an Sp-1 binding site, with the wild-type allele having five copies) that result in a decreased transcriptional activity. In patients with asthma, only those individuals that expressed the wild-type 5-LO promoter responded well to therapy with a 5-LO inhibitor (ABT-761, the drug was never marketed), whereas individuals with both 5-LO promoter alleles mutated showed no significant improvement of lung function when treated. It has not yet been examined whether these mutations also affect the responses of asthma patients to leukotriene receptor antagonists (e.g. montelukast, zafirlukast).

Sanak et al. described a polymorphism within the leukotriene C4 synthase promoter that resulted in higher risk of
aspirin-induced asthma. This genetic variant may also alter response to treatment with drugs directed against leukotrienes [30].

In conclusion, the studies by Drazen et al. [29] and Drysdale et al. [24] in particular indicate that genetic testing may help to predict drug response and may eventually be used to optimize individual pharmacotherapy.

**Genetics of host-defence**

Apart from pharmacogenetic studies, the analysis of gene–environment interactions to date is hypothesis driven. The difficulties in quantifying and characterizing environmental risk factors for atopy (including onset and length of period of exposure) make these studies a challenge. Very high numbers of affected and unaffected subjects carefully characterized (longitudinally) for both the environmental setting and disease expression may be required to test for interactions between genetic variants and non-genetic influences.

However, recent genetic studies support the ‘hygiene hypothesis’, which postulates that atopy may be the result of a misdirected immune response in the absence of infection.

First, resistance to *Schistosoma mansoni* [31] and *Plasmodium falciparum* blood levels [32] (two independent studies) were linked to chromosome 5q31-33, a region (containing the IL-4 cytokine gene cluster) that has shown strong evidence for linkage to atopy-associated traits. Furthermore, a major locus closely linked to the interferon-γ receptor gene appears to control the switch from a T helper 2 to a T helper 1 cytokine profile during *S. mansoni* infection [33,34].

Second, SNPs within the FcεRI-β gene have been related to increased total serum IgE levels in heavily parasitized Australian aborigines, indicating a protective role in parasitic infection [35]. These SNPs have also been related to asthma, bronchial hyperresponsiveness, AD and atopy (see Supplementary Table 3). FcεRI-β maps to 11q13, a region that showed evidence for linkage to asthma and associated traits in multiple studies (Supplementary Table 3).

Finally, a polymorphism in the β2AR encoding gene (Arg16) that has been related to asthma (see Supplementary Table 3) was also associated with higher levels of parasitic infection [36].

**Ethnic differences in ‘host defense’ and ‘atopy’ genes**

Evolutionary pressure with regard to infectious agents has differed significantly between continents. Significant ethnic differences in genes involved in immune defense mechanisms have been reported and may be based on differences in natural selection over the past centuries. Racial differences in genes involved in both host defense and allergic inflammation can best be demonstrated for CC chemokines and their receptors. CC chemokines have been shown to be crucial mediators of the allergic inflammation due to their potent chemoattractant properties for eosinophils, basophils and T cells [37]. Observations with regard to ethnic differences are as follows.

Evidence for linkage to chromosome 17q11.2 (a region that contains the CC chemokine gene cluster) has been reported in African Americans [38] but not in any Caucasian population (Supplementary Table 1).

A 32 base pair deletion in the CC chemokine receptor CCR5 renders individuals resistant to infection with macrophage-tropic HIV strains. This mutation is found in >10% of Caucasians, whereas it cannot be found in African populations [39]. A reduced risk of asthma was reported for carriers of the CCR5 deletion [40]. However, this could not be confirmed by Mitchell et al. [41].

In contrast to Caucasian individuals, the Duffy Antigen/Receptor for Chemokines is not expressed on red blood cells in the vast majority of African people (a point mutation in the Duffy promoter abolishes erythrocyte gene expression). This confers an evolutionary advantage since Duffy-negative erythrocytes are resistant to infection by *Plasmodium vivax*, which is endemic in most of Africa. Duffy has been shown to bind with high affinity to chemokines of both the CXC and CC classes, and is believed to function as a clearance receptor for chemokines (reviewed in [42]). It can therefore be hypothesized that higher or longer exposure to chemokines due to the absence of Duffy on erythrocytes might contribute to asthma pathogenesis in subjects of African descent.

A functional mutation in the proximal promoter of the CC chemokine RANTES was significantly more frequent among individuals of African descent compared with Caucasian subjects [43]. This mutation was associated with AD [43], asthma and atopy [44].

The 3’ untranslated region of eotaxin has shown a much higher degree of polymorphism in African American and Afro-Caribbean individuals than in Caucasians. Polymorphic alleles were in linkage disequilibrium with asthma in both African American and Afro-Caribbean families, but not in Caucasian families [45].

Ethnic differences have also been described for various other genes involved in the allergic inflammation (e.g. IL-4Rα [21], β2AR [24]). We can therefore speculate that inconsistent findings in the genetic studies of asthma and atopy summarized in this article may partly be explained by ethnic differences in nature and frequencies of genetic
variants in disease susceptibility genes. We can also speculate that ethnic differences in inflammatory genes (in addition to environmental factors) may also underlie the significant worldwide differences in the prevalence of asthma, allergic rhinitis, and AD [46].

Conclusion
Asthma and atopy are complex, multifactorial disorders. Major strides have been made in identifying chromosomal regions and candidate genes linked to asthma. However, the significant increase in the prevalence of atopy-related disorders over the past decades cannot be explained by changes in gene frequencies. It is rather probable that various pre-existing genetic factors interacting with a dramatically changing environment (decline of infectious diseases, changes in diet, immunizations, and others) have rendered a large percentage of the population susceptible to asthma and atopy. Genetic variations that evolved to improve resistance to infections may very probably be misdirected to promote allergic inflammation in the absence of infection in Western societies. Redundancies in host defense mechanisms may explain the large number of chromosomal regions as well as a steadily growing number of genetic variants related to atopy. Inconsistent findings summarized in this article may be explained by ethnic differences in host defense genes, but also by limitations to taking gene–gene as well as gene–environment interactions into account. Large prospective, multicenter studies, in addition to retrospective collaborations as described previously [14], may help to better understand genetic and environmental risk factors for atopy.

Acknowledgement
This article was supported by BMBF grant 01G0002.

References
1. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH: Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994, 149: 358-364.
2. von Mutius E, Braun-Fahrlander C, Schierl R, Riedler J, Ehlersmann S, Maisch S, Waser M, Nowak D: Exposure to endotoxin or other bacterial components might protect against the development of atopy. Clin Exp Allergy 2000, 30:1230-1234.
3. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann HH: Skin test reactivity and number of siblings. BMJ 1994, 308:692-695.
4. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R: Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy 2000, 30:197-193.
5. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, Wahn U: Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ 2001, 322:390-395.
6. Gereda JE, Leung DY, Thatayatkam A, Streib JE, Price MR, Kleinerman N, Liu AH: Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. Lancet 2000, 355:1680-1683.
7. Sandford A, Weir T, Pare P: The genetics of asthma. Am J Respir Crit Care Med 1996, 153:1749-1765.
8. Skadhauge LR, Christensen K, Kiyvik KO, Sigsgaard T: Genetic and environmental influence on asthma: a population-based study of 11,688 Danish twin pairs. Eur Respir J 1999, 13:8-14.
9. Lander ES, Schork NJ: Genetic dissection of complex traits. Science 1994, 265:2037-2048.
10. Barnes KC: Atopy and asthma genes—where do we stand? Allergy 2000, 55:803-817.
11. Cookson W: The alliance of genes and environment in asthma and allergy. Nature 1999, 402:B5-B11.
12. Ober C, Moffatt MF: Contributing factors to the pathobiology. The genetics of asthma. Clin Chest Med 2000, 21:245-261.
13. Palmer LJ, Cookson WO: Genomic approaches to understanding asthma. Genome Res 2000, 10:1280-1287.
14. Lonjou C, Barnes K, Chen H, Cookson WO, Deichmann KA, Hall IP, Holloway JW, Latinen T, Palmer LJ, Wjst M, Morton NE: A first trial of retrospective collaboration for positional cloning in complex inheritance: a search for the cytokine region on chromosome 5 by the consortium on asthma genetics (COAG). Proc Natl Acad Sci USA 2000, 97:10942-10947.
15. Palmer LJ, Lonjou C, Barnes K, Chen H, Cookson WO, Deichmann KA, Holloway JW, Latinen T, Wjst M, Morton NE: Special Reprint: A retrospective collaboration on chromosome 5 by the International Consortium on Asthma Genetics (COAG). Clin Exp Allergy 2001, 31:152-154.
16. Becker KG, Simon RM, Bailey-Wilson JE, Freidlin B, Biddon WE, McFarland HF, Trent JM: Clustering of non-major histo-compatibility complex susceptibility candidate loci in human autoimmune diseases. Proc Natl Acad Sci USA 1998, 95:9979-9984.
17. Cookson WO, Ubbi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, Coleman R, Leahey NL, Trombat RC, Moffat MF, Harper JT: Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. Nat Genet 2001, 27:372-373.
18. Lee YA, Wahn U, Kehr H, Tarani L, Busino LC, Gustafsson D, Andersson F, Oranje AP, Wolkkertorfer A, Berg A, Hoffmann U, Kustner W, Wienker T, Ruschendorf F, Reis A: A major susceptibility locus for atopic dermatitis maps to chromosome 5q21. Nat Genet 2000, 26:470-473.
19. Graves PE, Kabesch M, Halonen M, Holberg CJ, Baldini M, Fritschach C, Weiland SK, Erickson RP, von Mutius E, Martinez FD: A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children. J Allergy Clin Immunol 2000, 105:506-513.
20. Kruse S, Japha T, Tedner M, Sparholt SH, Forster J, Kuehr J, Deichmann KA: The polymorphism S503P of the interleukin-4 receptor alpha gene is associated with atopy and influence the signal transduction. Immunology 1999, 96:385-371.
21. Ober C, Leavitt SA, Tsalenko A, Howard TD, Hoki DM, Daniel R, Ober C, Moffatt MF: The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. Immunology 1999, 96:385-371.
22. Barnes KC, Mathias RA, Nickel R, Freidhoff LR, Stockton ML, Xue X, Naidu RP, Levett PN, Casolaro V, Beaty TH: Testing for gene–gene interaction controlling total IgE in families from Barbados: Evidence of sensitivity regarding linkage heterogeneity among families. Genomics 2001, 71:246-251.
23. Hall IP: Pharmacogenetics of asthma. Eur Respir J 2000, 15:449-451.
24. Drysdale CM, McGraw DW, Stack CB, Stephens JC, Judson RS, Nandabalan K, Arnold K, Ruano G, Liggett SB: The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. Immunology 1999, 96:385-371.
25. Ober C, Leavitt SA, Tsalenko A, Howard TD, Hoki DM, Daniel R, Newman DL, Wu X, Parry R, Lester LA, Solway J, Blumenthal M, King RA, Xu J, Meyers DA, Bleecker ER, Cox NJ: Variation in the interleukin 4-receptor alpha gene confers susceptibility to asthma and atopy in ethnically diverse populations. Am J Hum Genet 2000, 66:517-526.
26. Barnes KC, Mathias RA, Nickel R, Freidhoff LR, Stockton ML, Xue X, Naidu RP, Levett PN, Casolaro V, Beaty TH: Testing for gene–gene interaction controlling total IgE in families from Barbados: Evidence of sensitivity regarding linkage heterogeneity among families. Genomics 2001, 71:246-251.
27. Hall IP: Pharmacogenetics of asthma. Eur Respir J 2000, 15:449-451.
CN: The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med 2000, 162:75-80.

28. Yan L, Gaisinsky RE, Bernstein JA, Liggett SB, Weinshilboum RM: Histamine N-methyltransferase pharmacogenetics: association of a common functional polymorphism with asthma. Pharmacogenetics 2000, 10:261-266.

29. Drazen JM, Yandava CN, Dubé L, Szczeklik A, Hippensteel R, Pillai A, Israel E, Schork N, Silverman ES, Katz DA, Drajesk J: Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. Nat Genet 1999, 22:168-170.

30. Sanak M, Pierzchalska M, Bazan-Socha S, Szczeklik A: Enhanced expression of the leukotriene C(4) synthase due to overactive transcription of an allelic variant associated with aspirin-intolerant asthma. Am J Respir Cell Mol Biol 2000, 23:290-296.

31. Marquet S, Abel L, Hillaire D, Dessein H, Kaili J, Feingold J, Weissenbach J, Dessein AJ: Genetic localization of a locus controlling the intensity of infection by Schistosoma mansoni on chromosome 5q31-q33. Nat Genet 1996, 14:181-184.

32. Rihet P, Traore Y, Abel L, Aucan C, Traore-Leroux T, Fumoux F: Malaria in humans: Plasmodium falciparum blood infection levels are linked to chromosome 5q31-q33. Am J Hum Genet 1998, 63:498-505.

33. Dessein AJ, Hillaire D, Elwali NE, Marquet S, Mohamed-Ali Q, Mirghani A, Henri S, Abdelhameed AA, Saeed OK, Magzoub MM, Abel L: Severe hepatic fibrosis in Schistosoma mansoni infection is controlled by a major locus that is closely linked to the interferon-gamma receptor gene. Am J Hum Genet 1999, 65:709-721.

34. Roberts M, Butterworth AE, Kimani G, Kamau T, Fulford AJ, Dunne DW, Ouma JH, Sturrock RF: Immunity after treatment of human schistosomiasis: association between cellular responses and resistance to reinfection. Infect Immun 1993, 61:4984-4993.

35. Palmer LJ, Pare PD, Faux JA, Moffatt MF, Daniels SE, LeSouef PN, Bremner PR, Mockford E, Gracey M, Spargo R, Musk AW, Cookson WO: Fc epsilon R1-beta polymorphism and total serum IgE levels in endemically parasitized Australian aborigines. Am J Hum Genet 1997, 61:182-188.

36. Ramsay CE, Hayden CM, Tiller KJ, Burton PR, Hagel I, Palenque M, Lynch NR, Goldblatt J, LeSouef PN: Association of polymorphisms in the beta2-adrenoceptor gene with higher levels of parasitic infection. Hum Genet 1999, 104:269-274.

37. Nickel R, Beck LA, Stellato C, Schleimer RP: Chemokines and allergic disease. J Allergy Clin Immunol 1999, 104:723-742.

38. A genome-wide search for asthma susceptibility loci in ethnically diverse populations. The Collaborative diverse Study on the Genetics of Asthma (CSGA). Nat Genet 1997, 15:389-392.

39. Martinson JJ, Chapman NH, Rees DC, Liu YT, Clegg JB: Global distribution of the CCR5 gene 32-basepair deletion. Nat Genet 1997, 16:100-103.

40. Hall IP, Wheatley A, Christie G, McDougall C, Hubbard R, Helms PJ: Association of CCR5 delta32 with reduced risk of asthma. Lancet 1999, 354:1264-1265.

41. Mitchell TJ, Walley AJ, Pease JE, Venables PJ, Wiltshire S, Williams TJ, Cockson WO: Delta 32 deletion of CCR5 gene and association with asthma or atopy. Lancet 2000, 356:1491-1492.

42. Hadley TJ, Peiper SC: From malaria to chemokine receptor: the emerging physiologic role of the Duffy blood group antigen. Blood 1997, 89:3077-3091.

43. Nickel RG, Casaloro L, Vahm U, Beyer K, Barnes KC, Plunkett BS, Freidhoff LR, Sengler C, Plitt JR, Schleimer RP, Caraballo L, Naidu RP, Levett PN, Beaty TH, Huang SK: Atopic dermatitis is associated with a functional mutation in the promoter of the C-C chemokine RANTES. J Immunol 2000, 164:1612-1616.

44. Fryer AA, Spiteri MA, Bianco A, Hepple M, Jones PW, Strange RC, Makki R, Tavernier G, Smilie FL, Custovic A, Woodcock AA, Ollier WE, Hajeer AH: The –403 G → A promoter polymorphism in the RANTES gene is associated with atopy and asthma. Genes Immun 2000, 1:509-514.

45. Nickel R, Barnes KC, Sengler C, Casaloro L, Freidhoff LR, Weber P, Naidu R, Caraballo L, Ehrlich E, Plitt J, Schleimer RP, Huang SK, Beaty T: Evidence for linkage of chemokine polymorphisms to asthma in populations of African descent [abstract]. J Allergy Clin Immunol 1999, 103:S174.
Supplementary material

Supplementary Figure 1

Simplified cartoon of the allergic inflammation showing the mechanisms and molecules involved starting from antigen-presentation to organ-specific allergic reactions. Outlined are most candidate genes for atopy-associated phenotypes that have been analyzed to date (superscript numbers refer to Supplementary Table 3). APC, antigen presenting cell; AG, antigen; B7, costimulatory molecule B7; CC16, Clara cell protein 16; CCR5, CC chemokine receptor 5; CD, cluster of differentiation; CD40L, CD40 ligand; ECP, eosinophilic cationic protein; FcεR1-β, IgE receptor; GSTP1, glutathione-S-transferase 1; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; IRF-1, interferon regulatory factor 1; LT, leukotriene; LTC4, leukotriene C4 synthase; MBP, major basic protein; NO, nitric oxide; PAF, platelet activating factor; RANTES, regulated on activation, normal T cell expressed and secreted; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; Th, T helper cell.
### Supplementary Table 1

Results of genome-wide searches (asthma and associated traits)

| Study                  | Population | Individuals (n) | Sib-pairs (n) | 1q21         | 1p31         | 2pter        | 2q22-33      | 3q21         | 4q35         | 5p13-15      | 5q23-33      | 6p21.3-23    | 7p          |
|------------------------|------------|----------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------|
| CSGA 1 (1997)          | AA         | 117‡           | ns            | 172          | AD*          | Asthma*      | IgE*         |              |              |              |              |              |             |
|                        | C          | 215‡           | ns            | ns           |              | BHR*, RAST** |              |              |              |              |              |              |             |
|                        | H          | 48‡            | ns            | ns           |              |              |              |              |              |              |              |              |             |
| Hizawa et al. (1998)   | AA         | 281            | 172           |              |              |              |              |              |              |              |              |              |             |
|                        | C          | 299            | ns            |              |              |              |              |              |              |              |              |              |             |
|                        | H          | 281            |              |              |              |              |              |              |              |              |              |              |             |
| Daniels et al. (1996)  | AA         | 364            | ns            | 156          |              |              |              |              |              |              |              |              |             |
|                        | C          | 371/292        | ns            | 65           |              |              |              |              |              |              |              |              |             |
|                        | H          | 292            |              |              |              |              |              |              |              |              |              |              |             |
| Ober et al. (1998)     | AA         | 693            |              | 415          |              |              |              |              |              |              |              |              |             |
|                        | C          | 415            |              | 196          |              |              |              |              |              |              |              |              |             |
|                        | H          | 299            |              | 493          |              |              |              |              |              |              |              |              |             |
| Ober et al. (2000)     | AA         | 364            |              | 196          |              |              |              |              |              |              |              |              |             |
|                        | C          | 371/292        |              | 493          |              |              |              |              |              |              |              |              |             |
|                        | H          | 292            |              | 839          |              |              |              |              |              |              |              |              |             |
| Wjst et al. (1999)     | AA         | 693            |              |              |              |              |              |              |              |              |              |              |             |
|                        | C          | 693            |              |              |              |              |              |              |              |              |              |              |             |
|                        | H          | 693            |              |              |              |              |              |              |              |              |              |              |             |
| Yokouchi et al. (2000) | AA         | 415            |              |              |              |              |              |              |              |              |              |              |             |
|                        | C          | 415            |              |              |              |              |              |              |              |              |              |              |             |
|                        | H          | 415            |              |              |              |              |              |              |              |              |              |              |             |
| EGEA (2000)            | AA         | 493            |              |              |              |              |              |              |              |              |              |              |             |
|                        | C          | 493            |              |              |              |              |              |              |              |              |              |              |             |
|                        | H          | 493            |              |              |              |              |              |              |              |              |              |              |             |
| Lee et al. (2000)      | AA         | 839            |              |              |              |              |              |              |              |              |              |              |             |
|                        | C          | 839            |              |              |              |              |              |              |              |              |              |              |             |
|                        | H          | 839            |              |              |              |              |              |              |              |              |              |              |             |
| Cookson et al. (2001)  | AA         | 213            |              |              |              |              |              |              |              |              |              |              |             |
|                        | C          | 213            |              |              |              |              |              |              |              |              |              |              |             |
|                        | H          | 213            |              |              |              |              |              |              |              |              |              |              |             |

Continued overleaf
## Supplementary Table 1 Continued

| Population | Study | CSGA 1 (1997) | Hizawa et al. (1998) | Daniels et al. (1996) | Ober et al. (1998) | Ober et al. (2000)† | Wjst et al. (1999) | Yokouchi et al. (2000) | EGEA et al. (2000) | Lee et al. (2000) | Cookson et al. (2001) |
|------------|-------|---------------|----------------------|-----------------------|-------------------|--------------------|---------------------|---------------------|-------------------|------------------|---------------------|
|            |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
|            |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 8p23.3     |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 9 (DS1784) |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 11q13      |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 12q13-24.2 |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 13q11-32.2 |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 14q11.2-13 |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 14q32      |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 16q-tel    |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 16q23-24   |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 17p11.1-q11.2 |   |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 17q12-21   |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 17q25      |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 19q13      |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 20p        |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |
| 21q21      |       |               |                      |                       |                   |                    |                     |                     |                   |                  |                     |

AA, African American; AD, Atopic dermatitis; BHR, bronchial hyperresponsiveness; C, Caucasian; eos, eosinophil count; H, Hispanic; ns, not specified; RAST, radio allergo sorbent test; ST, positive skin test. *P ≤ 0.01, **P ≤ 0.001, ***P ≤ 0.0001. †Statistical significance (P ≤ 0.05) in both tests, likelihood ratio χ² test and transmission disequilibrium test. ‡ Only affected individuals, neither number of all individuals nor number of sib-pairs specified [17,18,38,S1–S7].
### Supplementary Table 2

Chromosomal regions showing evidence for linkage to asthma and related phenotypes

| Chromosomal region | Phenotype (linkage)                                | Population                      | Reference  |
|-------------------|----------------------------------------------------|---------------------------------|------------|
| 5q23-33           | Total IgE                                          | Dutch, Amish, Caucasian (UK)    | [S8–S10]   |
|                   | Total IgE, specific IgE, eosinophil count          | Australian                      | [S11]      |
|                   | Specific IgE                                       | African American                | [S12]*     |
|                   | Atopic dermatitis                                  | Caucasian (UK), German/Swedish  | [S13,S14]  |
|                   | Asthma/atopy                                       | Japanese                        | [S6,S15]*  |
|                   | Eosinophil count                                   | Caucasian (US)                  | [S16]      |
|                   | Hypereosinophilia                                  | Caucasian (US)                  | [S17]      |
|                   | Bronchial hyperresponsiveness                      | Dutch, Hutterites               | [S3,S18]*  |
| 6p21-23           | Specific IgE                                       | Caucasian (US)                  | [S1*,S19]  |
|                   | Asthma, IgE                                        | German/Swedish                  | [S5]*      |
|                   | Allergic asthma                                    | Colombian                       | [S20]      |
|                   | Eosinophil count                                   | Caucasian (Australian)          | [S2]*      |
| 11q13             | IgE                                                | Caucasian (UK)                  | [S21,S22]  |
|                   | IgE, positive skin test                            | Caucasian (Australian)          | [S2]*      |
|                   | Specific IgE                                       | Caucasian (Australian), African American | [S1*,S12]  |
|                   | Bronchial hyperresponsiveness, log IgE            | Caucasian (UK)                  | [S10]      |
|                   | Bronchial hyperresponsiveness                       | Caucasian                       | [S23]      |
|                   | Atopy                                              | Japanese                        | [S24]      |
|                   | Asthma, atopy                                      | Caucasian                       | [S25]      |
|                   | Atopic dermatitis                                  | German                          | [S26]      |
| 12q14-24          | Asthma                                             | German/Swedish Caucasain (US)   | [38,S27]*  |
|                   |                                                    | Caucasian (UK)                  | [S28]      |
|                   | Asthma, atopy                                      | Afro-Caribbean                  | [S29]      |
|                   | Total IgE, asthma                                  | Afro-Caribbean, Amish           | [S30]      |
|                   | Total IgE                                          | German                          | [S31]      |
|                   | Bronchial hyperresponsiveness                       | Hutterites                      | [S3]*      |
|                   | Eosinophil count                                   | French                          | [S7]*      |
| 13q11-32          | Atopic dermatitis                                  | German/Swedish                  | [S14]      |
|                   | Specific IgE                                       | Caucasian (UK)                  | [S1]*      |
|                   | Atopy                                              | Caucasian (Australian)          | [S2]*      |
|                   | Eosinophil count                                   | French                          | [S7]*      |
|                   | Asthma                                             | Caucasian (US), Japanese        | [38*,S6]*  |
|                   | Atopic asthma                                      | Japanese                        | [S32]      |

* Genome-wide searches.
## Supplementary Table 3

### Polymorphisms/mutations in candidate genes for asthma and related phenotypes

| Chromosomal location | Number* | Molecule                   | Single nucleotide polymorphism/mutation† | Phenotype related | Population       | Functional (in vitro) | Reference |
|----------------------|---------|----------------------------|------------------------------------------|-------------------|------------------|-----------------------|-----------|
| 1p32                 | 1       | Histamine-N-methyltransferase | C314T (Thr105Ile)                        | Asthma            | Caucasian        | Yes                   | [28]      |
| 2q33-34              | 2       | CD28                        | T19in3C                                  | None              | Caucasian        | [S33]                 |
|                      |         | CTLA-4                      | A49G                                     | None              | Caucasian        | [S33]                 |
|                      |         |                            | C-318T                                   | None              | Caucasian        |                       |           |
| 3p21                 | 3       | CCR5                        | CC5-332                                  | Asthma            | Caucasian        | Yes                   | [40]      |
| 5q31-34              | 4       | IL-4                        | C-590T (= C-589T)                        | Total IgE         | Japanese         | Yes                   | [S34]     |
|                      |         |                            |                                          | Specific IgE, wheeze | American        | [S35]                 |
|                      |         |                            |                                          | FEV1              | Caucasian        | [S36]                 |
|                      |         |                            |                                          | Atopic dermatitis | Japanese         | [S37]                 |
|                      |         |                            |                                          | None              | Caucasian        | [S38]                 |
|                      |         |                            |                                          | Total IgE         | Japanese         | [S39]                 |
|                      |         |                            |                                          | No Association    | British/Australian | [S40]                |
| 5                    |         | IL-5                        | C+33T                                    | None              | Australian       | [S41]                 |
| 6                    |         | IL-13                       | identical                                | Allergic asthma   | Dutch            | [S42]                 |
|                      |         |                            |                                          | Total IgE         | American/German  | [19]                  |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
| 7                    |         | β2-AR                       | identical                                | High IgE, atopic dermatitis | German       | [S43]                 |
|                      |         |                            |                                          | Atopic and intrinsic asthma | British/Japanese | [S44]                 |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
| 8                    | 8       | IRF-1                       | −300 G/T                                 | Drug response     | Caucasian/African American | Yes                   | [24]      |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
|                      |         |                            |                                          |                   |                  |                       |           |
| 9                    | 9       | CD14                        | −159 C → T                               | Total IgE         | Caucasian        | [S53]                 |
|                      |         |                            |                                          |                   | Hispanic         | [S54]                 |
|                      |         |                            |                                          |                   | British          | [S55]                 |
|                      |         |                            |                                          |                   | Japanese         | [S56]                 |
|                      |         |                            |                                          |                   |                  |                       |           |
| 10                   | 10      | LTC4 synthase               | −444 C                                   | Aspirin-induced asthma | Caucasian     | Yes                   | [30]      |

* Number indicates the number of alleles.
† Polymorphism/mutation refers to the nucleotide change or mutation in the gene.

Note: The table continues with additional entries for each column, including descriptions of the molecular changes, phenotypes related to these changes, populations studied, and references.
| Chromosomal location | Number* | Molecule | Single nucleotide polymorphism/mutation† | Phenotype related | Population | Functional (in vitro) | Reference |
|-----------------------|---------|----------|----------------------------------------|-------------------|------------|-----------------------|-----------|
| 6p21                  | 11      | HLA-II   | ~308 TNF2 LT-α                          | Specific IgE      | Multiple   | BHR                   | [S56]     |
|                       |         |          | LT alpha NcoI*1/                        |                   | Caucasian  | British               | [S57]     |
|                       |         |          | TNF-308*2 haplotype LT-alpha*2          |                   | British    |                       | [S58]     |
|                       |         |          | ~308 TNF1 LT-α                          |                   | Australian |                       | [S59]     |
| 6p21-12               | 24      | PAF-acetyl-hydrolase | Ile198Thr                    | Atopic Asthma/ total IgE | German/British | Yes                   | [S60]     |
|                       |         |          | Ala379Val Arg92His                      | Asthma/ specific IgE | Yes       | Yes                   |           |
| 10                    | 12      | 5-LO      | (GGGGCGG),<sub>−3−6</sub>              | Drug Response     | Not specified | Yes                   | [S29]     |
| 11q12-13              | 14      | CC16      | A38G                                    | Asthma            | British/Japanese | No                    | [S61]     |
|                       |         |          | Leu181/Leu183 E237G (= Gly237Glu)       | Atopy, BHR        | Australian | No                    | [S65]     |
|                       |         |          | none                                    |                   | Japanese   | No                    | [S64]     |
|                       |         |          | Rsal<sub>in2*B</sub> Rsal<sub>ex7</sub>+| Total IgE, atopic  | Australian | No                    | [S68]     |
|                       |         |          | Drug Response                           |                   | none       |                      |           |
|                       |         |          | FcrR1-β                                 | Atopy             | British    | Yes                   | [S62]     |
|                       |         |          |                                   |                   | Japanese   | No                    | [S63]     |
|                       |         |          | Leu181/Leu183 E237G (= Gly237Glu)       | Atopy, BHR        | Australian | No                    | [S65]     |
|                       |         |          | none                                    |                   | Japanese   | No                    | [S66]     |
| 12q13                 | 17      | STAT6     | G2964A                                  | Asthma            | Japanese   | No                    | [S72]     |
| 12q14                 | 16      | IFN-γ     | None                                    | Drug Response     | Not specified | Yes                   | [S61]     |
| 12q24                 | 18      | NO-synthase1 | (AAT)<sub>12</sub>                   | Drug Response     | Not specified | Yes                   | [S29]     |
| 14p11                 | 19      | TCR       | VA8.1(*)2                               | Specific IgE      | Caucasian  | No                    | [S75]     |
|                       |         |          | MCC BstXI                               | eczema            | Japanese   | No                    | [S76]     |
|                       |         |          |                                        |                   | none       | No                    | [S78]     |
|                       |         |          |                                        |                   | none       | No                    | [S79]     |
|                       |         |          |                                        |                   | none       | Japanese              | [S80]     |
|                       |         |          |                                        |                   | none       |                      |           |
|                       |         |          |                                        |                   | none       |                      |           |
| 16p12-p11             | 21      | IL-4Rα    | Q576R (= Arg551Gln)                     | Atopy, high IgE   | American   | Yes                   | [S81]     |
|                       |         |          |                                        |                   | Italian    | No                    | [S83]     |
|                       |         |          |                                        |                   | Japanese   | No                    | [S84]     |
|                       |         |          |                                        |                   | none       | No                    | [S85]     |
|                       |         |          |                                        |                   | none       | No                    | [S86]     |
|                       |         |          |                                        |                   | none       |                      |           |
|                       |         |          |                                        |                   | none       |                      |           |

Divergent positions of identical mutations are due to different database accession numbers used for reference. * Numbers refer to molecules in Supplementary Figure 1. † Nomenclature as in references. β<sub>2</sub>-AR, β<sub>2</sub> adrenergic receptor; BHR, bronchial hyperresponsiveness; CC16, Clara cell protein 16; CCR5, CC chemokine receptor 5; CD, cluster of differentiation; FcrR1-β, Fc epsilon receptor 1 beta (IgE receptor); FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; GSTP1, glutathione-S-transferase 1; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; IL-4/13 R, interleukin 4/13 receptor; IRF-1, interferon regulatory factor 1; 5-LO, 5-lipoxygenase; LT, leukotriene; LT-α, lymphotoxin α; LTC4, leukotriene C4 synthase; NO, nitric oxide; PAF, platelet activating factor; RANTES, regulated on activation, normal T cell expressed and secreted; STAT6, signal transducer and activator of transcription 6; TCR, T-cell receptor; TNF, tumor necrosis factor.
2q33 are not associated with asthma or atopy. Eur J Immunogenet 2000, 27:57-61.

S34. Noguchi E, Shibasaki M, Arinami T, Takeda K, Yokouchi Y, Kawashima T, Yanagi H, Matsui A, Hamaguchi H: Association of asthma and the interleukin-4 promoter gene in Japanese. Clin Exp Allergy 1998, 28:449-453.

S35. Rosenwein LJ, Klemm DJ, Dresbach JK, Inamura H, Mascali JJ, Klinert M, Boriah L: Promoter polymorphisms in the chromosome 5q gene cluster in asthma and atopy. Clin Exp Allergy 1995, 25(suppl 2):74-78, [discussion] 95-76.

S36. Walley AJ, Cookson WO: Investigation of an interleukin-4 promoter polymorphism for associations with asthma and atopy. J Med Genet 1996, 33:689-692.

S37. van der Pouw Kraan TC, van Veen A, Boeije LC, van Tuyl SA, de Groot ER, Stapel SO, Bakker A, Verweij CL, Aarden LA, van der Zee JS: An IL-13 promoter polymorphism associated with increased risk of allergic asthma. Genes Immun 1999, 1:61-65.

S38. Kawai M, Shimazu S, Sasaki S, Adra CN, Kitaichi M, Inoue H, Yamauchi S, Yandora C, Drazen JM: An IL13 coding region variant is associated with a high total serum IgE level and atopic dermatitis in the German multicenter atopy study (MAS-90). J Allergy Clin Immunol 2000, 106:167-170.

S39. van der Pouw Kraan TC, van Veen A, Boeije LC, van Tuyll SA, de Groot ER, Stapel SO, Bakker A, Verweij CL, Aarden LA, van der Zee JS: An IL-13 promoter polymorphism associated with increased risk of allergic asthma. Genes Immun 1999, 1:61-65.

S40. Laing IA, Goldblatt J, Eber E, Hayden CM, Rye PJ, Gibson NA, Palmer LJ, Burton PR, Le Souef PN: A polymorphism of the CC16 gene is associated with an increased risk of asthma. Clin Exp Allergy 1998, 28:578-584.

S41. Murray RL, Williams BG, Calafat AM, Kligman EL, Kannan K, Davis LE, Gladen BC, Wennberg RL, Howard PA, Bielanski BL et al.: Association of polymorphisms within the tumour necrosis factor alpha promoter region with asthma and atopy. Br J Clin Pharmacol 2000, 49:549-559.

S42. Summerhill E, Leavitt SA, Gidley H, Parry R, Solway J, Ober C: Beta(2)-adrenergic receptor Arg16/Glu16 genotype is associated with reduced lung function, but not with asthma, in the Hutterites. Am J Respir Crit Care Med 2000, 162:599-602.

S43. Hologic JW, Dunbar PR, Riley GA, Cookson WO, Hopkin JM: Fc epsilon RI-beta polymorphism and risk of atopy in a general population sample. BMJ 1995, 311:776-779.

S44. Duflou R, Wilkinson J, Wheatley A, Thomas NS, Doull I, Morton N, Lio P, Harvey JF, Liggett SB, Holgate ST, Hall IP: The glutamine 27 beta(2)-adrenergic receptor polymorphism is associated with elevated IgE levels in asthmatic families. J Allergy Clin Immunol 1997, 100:261-265.

S45. Li, Kam WA, Mansur AH, Britton J, Williams G, Padvorl I, Richards K, Campbell DA, Morton N, Holgate ST, Morrison JJ: Association between 308 tumour necrosis factor promoter polymorphism and bronchial hyperreactivity in asthma. Clin Exp Allergy 1999, 29:1204-1208.

S46. Moffatt MF, Cookson WO: The genetics of specific allergy. Monogr Allergy 1996, 33:71-96.

S47. Gao PS, Mao XQ, Kawai M, Enomoto T, Sasaki S, Tanabe O, Yoshimura K, Shaldon SR, Dake Y, Kitaichi M, Coulp P, Shirakawa T, Hopkin JM: Negative association between asthma and variants of CC16(CC10) on chromosome 11q13 in British and Japanese populations. Hum Genet 1998, 103:57-59.

S48. Shiraikawa T, Li A, Dubowitz M, Dekker JW, Shaw AE, Faux JA, Ra C, Cookson WO: Association between atopy and variants of the beta subunit of the high-affinity immunoglobulin E receptor. Nat Genet 1994, 7:125-129.

S49. Shiraikawa T, Mao XQ, Sasaki S, Enomoto T, Kawai M, Morimoto K, Hopkin J: Association between atopic asthma and a coding variant of Fc epsilon RI beta in a Japanese population [letter]. Hum Mol Genet 1996, 5:2068.

S50. Hill MR, James AL, Faux JA, Ryan G, Hopkin JM, Le Souef P, Musk AW, Cookson WO: Fc epsilon RL-beta polymorphism and risk of atopy in a general population sample. BMJ 1995, 311:776-779.

S51. Saito NN, Whelan P, Lio P, Harvey JF, Liggett SB, Holgate ST, Hall IP: The glutamine 27 beta2-adrenergic receptor polymorphism with lower airway reactivity in asthmatic subjects. Lancet 1995, 345:1212-1214.
S70. Hizawa N, Yamaguchi E, Jinushi E, Kawakami Y: A common FCER1B gene promoter polymorphism influences total serum IgE levels in a Japanese population. *Am J Respir Crit Care Med* 2000, 161:906-909.

S71. Fryer AA, Bianco A, Heppe M, Jones PW, Strange RC, Spiteri MA: Polymorphism at the glutathione S-transferase GSTP1 locus. A new marker for bronchial hyperresponsiveness and asthma. *Am J Respir Crit Care Med* 2000, 161:1437-1442.

S72. Gao PS, Mao XO, Roberts MH, Annobu Y, Akama W, Enomoto T, Dake Y, Kawai M, Sasaki S, Hamasaki N, Iizhara K, Shirakawa T, Hopkin JM: Variants of STAT6 (signal transducer and activator of transcription 6) in atopic asthma. *J Med Genet* 2000, 37:380-382.

S73. Hayden C, Pereira E, Rye P, Palmer L, Gibson N, Palenque M, Hagel I, Lynch N, Goldblatt J, Lesouef P: Mutation screening of interferon-gamma (IFNgamma) as a candidate gene for asthma. *Clin Exp Allergy* 1997, 27:1412-1416.

S74. Wechsler ME, Grasemann H, Deykin A, Silverman EK, Yandava CN, Israel E, Wand M, Drazen JM: Exhaled nitric oxide in patients with asthma. Association with nos1 genotype. *Am J Respir Crit Care Med* 2000, 162:2043-2047.

S75. Moffatt MF, Schou C, Faux JA, Cookson WO: Germline TCR-A restriction of immunoglobulin E responses to allergen. *Immunogenetics* 1997, 46:226-230.

S76. Mao XO, Shirakawa T, Yoshikawa T, Yoshikawa K, Kawai M, Sasaki S, Enomoto T, Hashimoto T, Furuyama J, Hopkin JM, Morimoto K: Association between genetic variants of mast-cell chymase and eczema. *Lancet* 1996, 348:581-583.

S77. Mao XO, Shirakawa T, Enomoto T, Shimazu S, Dake Y, Kitano H, Hagihara A, Hopkin JM: Association between variants of mast cell chymase gene and serum IgE levels in eczema. *Hum Hered* 1998, 48:38-41.

S78. Kawashima T, Noguchi E, Arinami T, Kobayashi K, Otsuka F, Hamaguchi H: No evidence for an association between a variant of the mast cell chymase gene and atopic dermatitis based on case-control and haplotype-relative-risk analyses. *Hum Hered* 1998, 48:271-274.

S79. Pascale E, Tarani L, Meglio P, Businco L, Battiloro E, Cimino-Reale G, Verna R, D’Ambrosio E: Absence of association between a variant of the mast cell chymase gene and atopic dermatitis in an Italian population. *Hum Hered* 2001, 51:177-179.

S80. Tanaka K, Sugiura H, Uehara M, Sato H, Hashimoto-Tamaoki T, Furuyama J: Association between mast cell chymase genotype and atopic eczema: comparison between patients with atopic eczema alone and those with atopic eczema and atopic respiratory disease. *Clin Exp Allergy* 1999, 29:800-803.

S81. Hershey GK, Friedrich MF, Easwein LA, Thomas ML, Chatila TA: The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med* 1997, 337:1720-1725.

S82. Rosa-Rosa L, Zimmermann N, Bernstein JA, Rothenberg ME, Khuwana Hershey GK: The R576 IL-4 receptor alpha allele correlates with asthma severity. *J Allergy Clin Immunol* 1999, 104:1008-1014.

S83. Patuzzo C, Trabetti E, Malerba G, Martinati LC, Boner AL, Pescoliderungg L, Zanoni G, Pignatti PF: No linkage or association of the IL-4Ralpha gene Q576R mutation with atopic asthma in Italian families. *J Med Genet* 2000, 37:382-384.

S84. Oiso N, Fukai K, Ishii M: Interleukin 4 receptor alpha chain polymorphism Gin551Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol* 2000, 142:1003-1006.

S85. Mitsuayasu H, Iizhara K, Mao XO, Gao PS, Aninobu Y, Enomoto T, Kawai M, Sasaki S, Dake Y, Hamasaki N, Shirakawa T, Hopkin JM: Ile50Val variant of IL4R alpha upregulates IgE synthesis and associates with atopic asthma. *Nat Genet* 1998, 19:119-120.

S86. Noguchi E, Shibasaki M, Arinami T, Takeda K, Yokouchi Y, Kobayashi K, Iizhara K, Nakahara S, Matsui A, Hamaguchi H: No association between atopy/asthma and the Ile50Val polymorphism of IL-4 receptor. *Am J Respir Crit Care Med* 1999, 160:342-345.