

Genetic aspects of atopic allergy

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Atopy and the associated clinical disorders of asthma, rhinitis, and infantile eczema are familial, and are due to the interaction between strong genetic and environmental factors. The discovery of genetic factors which predispose to asthma will allow better classification of asthma into subtypes with distinct clinical courses and responses to therapy. Asthma and allergic diseases may become preventable once the precise recognition of children at genetic risk is possible. Eventually, genetic discoveries will lead to new pharmacologic treatments for allergic disorders.

Although the genetics of asthma and atopy is very complex, many of the difficulties are now understood, and the full characterization of the genes which underlie these conditions is achievable. Some genes have already been identified, and a consensus is emerging of the position of several chromosomal regions which contain asthma and atopy-associated genes.

Genes predispose to atopy or asthma because their DNA sequences contain polymorphisms (variants) which alter gene function. In single-gene disorders, these variants usually destroy gene function and are known as mutants. For disorders as common as atopy, the underlying changes in the DNA may lead to more subtle changes in gene function or expression.

Genes causing disease may be identified either by the process known as “positional cloning”, or by examining candidate genes. Positional cloning relies on the demonstration of genetic linkage (coinheritance) of disease and genetic markers of known chromosomal localization. Once linkage is established, the linked region can be dissected by further genetic mapping with a dense array of closely linked markers. Genetic mapping is followed by “physical mapping”, the assembly of

overlapping DNA clones covering the linked regions, and the eventual identification and sequencing of genes from the DNA.

Positional cloning has the advantage of not requiring any pre-existing knowledge of the pathophysiology of the disease being studied. However, the power to detect linkage in complex genetic diseases is very limited, so that several thousand two-generation families may be necessary to detect linkage to a gene affecting 10% of the subjects with disease. In the case of atopy, the position is further confounded by the presence of maternal effects, a high population prevalence, strong environmental factors, and variable penetrance of the traits (1).

Candidate genes are genes which are already known to be involved in the pathways contributing to disease. The role of candidate genes may be assessed by defining polymorphisms within the respective genes, and testing for associations with disease. Associations may be found even if the polymorphisms do not alter the function of a gene, because when a new mutation or variant first arises in a gene, it will be physically associated or linked with polymorphisms (alleles) of other sequences on the same chromosome. This association of alleles on a chromosome is called “linkage disequilibrium”. Within a gene, linkage disequilibrium of alleles persists for hundreds of generations, so that nonfunctional alleles will serve as surrogates for the functional sequences nearby. The testing of candidate genes can be difficult, because of uncertainty whether a polymorphism is functional or not, if, for example, it occurs in the promoter region of a gene, or within the introns.

The complexity of the cytokine networks that modulate atopy and inflammation means that a plausible case could be put for as many as 100 different candidate genes. Therefore, successful

identification of genes predisposing to asthma is likely to depend on a combination of positional cloning and candidate gene strategies.

Genes may cause susceptibility to atopy and asthma through a number of different pathways. They may predispose in general to atopy, or they may influence the specific IgE response to individual allergens, or influence bronchial hyperresponsiveness independently of atopy. Finally, they may enhance inflammation independently of atopic mechanisms.

Genes predisposing to atopy

Fc ϵ RI β on chromosome 11q

Chromosome 11q13 was the first genetic region linked to atopy (2). The results of this study were at first considered controversial (3), largely because attempts at replication used the lod statistic inappropriately and tested very small sample sizes. Linkage to the region has now been replicated consistently (4–8). The linkage has been confounded by the high prevalence of atopy and maternal effects (9, 10).

Recognition of the maternal effect allowed fine mapping of the atopy locus (10, 11), and the localization of the beta chain of the high-affinity receptor for IgE (Fc ϵ RI β) near to the putative atopy gene (10).

Two coding polymorphisms (Fc ϵ RI β *Leu181* and Fc ϵ RI β *Leu181/Leu183*) were identified within the gene at the beginning of exon 6 (12). Both showed strong associations with atopy when maternally inherited, and seemed quite common (12). However, a study of 1000 subjects found the population prevalence of Fc ϵ RI β *Leu181/Leu183* to be only 4%, and Fc ϵ RI β *Leu181* was not found at all (13). Subsequently, both variants have been very difficult to detect, and their status is currently uncertain. The region contains members of a gene family including *Htm4* (14) and *CD20* (11, 14), suggesting the possibility of homologous sequences in unknown genes or pseudogenes confounding the detection of the variants.

A further coding variant in the gene, *E237G*, has also been described. It also is associated with atopy and bronchial hyperresponsiveness (15). It is present in approximately 5% of the UK and other European populations. It has been found in 20% of Japanese asthmatics (16). It is not clear whether *E237G* is functionally important, or whether it is in disequilibrium with some other polymorphism which does alter gene function.

Two noncoding single nucleotide polymorphisms (SNPs) have been identified within the gene. Although they do not obviously alter gene function,

they have shown very strong associations with atopic eczema in a study of 150 families identified through children with eczema (17). Strong associations were also found to asthma in the same families, (17). The *E237G* variant was not present in these families, and the functional sequences predisposing to eczema have not yet been identified.

The cytokine cluster on chromosome 5

The 5q23–31 region contains several molecules implicated in the pathogenesis of asthma and the control of IgE. These include the genes coding for interleukins (IL)-3, -4, -5, -9, -12b, and -13, the glucocorticoid receptor, and the β_2 -adrenergic receptor.

In Amish families, Marsh et al. found that there was linkage between total IgE levels and several markers in this region; namely, IL-4R, IRF-1, IL-9, D5S393, and D5S399 (18). IL-4R showed the strongest linkage when those subjects with antigen-specific responses were excluded (18). The results were confirmed by Meyers et al. in Dutch families who showed linkage of total IgE levels to IL-9, D5S393, D5S436, and CSF-1R (19). Linkage in the same families to bronchial hyperresponsiveness was also observed (20, 21). The claim that this region accounted for 78% of the genetic predisposition to high IgE levels (22) has not been substantiated in other studies.

In another study, Doull et al. found significant allelic association between the 118 allele of the IL-9 microsatellite and total serum IgE (23). Our group have found weak linkage between total serum IgE and bronchial hyperresponsiveness in this region, but have found a significant linkage to blood eosinophil counts (24). Allelic associations were demonstrated between microsatellite markers and various phenotypes; in particular, IL-4RP1 and the eosinophil count, and IL-9 and bronchial hyperresponsiveness. The IL-9 association was with a different allele from that reported by Doull et al. (23).

At present, there is evidence only for one polymorphism being functional in the 5q cytokine cluster, in the IL-4 promoter (25). We have investigated this polymorphism for associations with asthma and atopy phenotypes (26) and found a weak association with specific IgE to house-dust mite (HDM) (*Dermatophagoides pteronyssinus*) in an Australian population sample.

Overall, the results suggest that several genes from this region are interacting in the pathogenesis of atopy. Their identification remains a formidable task.

Chromosome 12

The presence of the genes for interferon-gamma and stem cell factor (also known as mast-cell growth

factor) makes this region an attractive candidate for asthma and atopy susceptibility loci. Barnes et al. (27) have recently reported the linkage of asthma and total serum IgE concentrations on chromosome 12q in two sets of families; 29 Afro-Caribbean families (ascertained through asthmatic probands) and 11 Amish kindreds. Linkage was detected in the Afro-Caribbean families to asthma at D12S379 ($P=0.001$) and total serum IgE at D12S360 ($P=0.001$). The Amish population showed replication at a lower level of significance for total serum IgE at D12S360 ($P=0.01$). The investigators went on to perform a multipoint analysis of asthma in the Afro-Caribbean families showing a peak of linkage close to D12S379 ($P=0.003$). The results have recently been replicated in the families of German schoolchildren selected for high total serum IgE concentrations (28).

The IL-4 receptor on chromosome 16

An association has recently been reported between atopy and a gain-of-function polymorphism in the alpha subunit of the IL-4 receptor on chromosome 16 (29). An adenine to guanine substitution at nucleotide 1902 results in arginine rather than glutamine at position 576 (R576). This allele was associated with enhanced signalling of the IL-4 receptor and increased CD23 expression. In a limited sample, the R576 allele was found in 4/7 patients with severe atopic dermatitis, and in 13/20 subjects with atopy compared to 5/30 without atopy. Genetic linkage and association of microsatellites in this region have been independently identified (30). The overall importance of this genetic effect has yet to be tested in large samples.

Genes influencing specific IgE responses to particular allergens

Atopic subjects differ in the particular allergens to which they react. This difference is of clinical significance, as asthma and bronchial hyperresponsiveness are associated with allergy to HDM, but not grass pollens (31). It is therefore of interest to examine whether particular genes influence the IgE response to specific allergens.

The genes encoding the human leukocyte antigen (HLA) proteins, and the genes for the T-cell receptor (TCR) are central to the handling and recognition of foreign antigen. Consequently, these genes are plausible candidates for constraining specific IgE reactions.

HLA

The human major histocompatibility complex (MHC) includes genes coding for HLA class II

molecules (HLA-DR, DQ, and DP), which are involved in the recognition and presentation of exogenous peptides.

An HLA influence on the IgE response was first noted by Levine et al. (32), who found an association between HLA class I haplotypes and IgE responses to antigen E derived from ragweed allergen (*Ambrosia artemisiifolia*). This association has been subsequently found to be due to restriction of the response to a minor component of ragweed antigen (Amb a 5) by HLA-DR2 (33). This association has been confirmed (34).

Many other possible positive (35–39) and negative (40–42) MHC associations with allergen reactivity have been described. The overall effect of the MHC on allergens seems to be a multiplicity of small effects, usually conferring a relative risk of less than 2 (43).

Stronger HLA effects may be seen when the antigen is small, as in the case of aspirin-induced asthma (AIA). This disease shows a fourfold increase in the frequency of DPB1*0301 compared to controls (44).

The T-cell receptor (TCR)

The T-cell receptor is usually made up of α and β chains, although 5% of receptors consist of γ and δ chains. The β chain locus is on chromosome 7, and the α chain locus is on chromosome 14. The δ chain genes are found within the α chain locus. The usage of the TCR V α and V β segments by lymphocytes is not random, and may be under genetic control (45–48).

We have shown genetic linkage between IgE responses and microsatellites from the TCR- α/δ region, but not the TCR- β region (49). Two independent sets of families, one British and one Australian, were investigated. Significant linkage of IgE responses to the HDM allergens Der p 1 and Der p 2, and the cat allergen Fel d 1, and the total serum IgE to TCR- α/δ was seen in both family groups. The results show that a locus in the TCR α/δ region is modulating IgE responses. The close correlation between total and specific IgE makes it difficult to determine whether the locus controls specific IgE reactions to particular allergens or confers generalized IgE responsiveness. Nevertheless, linkage was strongest with highly purified allergens, suggesting that the locus primarily influences specific responses.

The degree of linkage disequilibrium across the TCR- α/δ locus is low (50), and the microsatellite has been localized only within a 900-kb yeast artificial chromosome (51). Therefore, the observed linkage may be with any elements of TCR- α or TCR- δ , or with other genes in the locality.

Several V α genes have been found to be polymorphic (52), and limitation of the response to an allergen may correspond to these polymorphisms. Particular TCR-V α usage may induce IL-4-dominant (Th2) helper T-cells, which enhance IgE production (53). A reported nonrandom usage of V α 13 in Lol p 1-specific T-cell clones supports independently the hypothesis of V α genes controlling IgE responses (54).

We have recently found that a polymorphism in V α 8.1 shows strong association with IgE responses to Der p 2, and that there is strong genetic interaction between these alleles and HLA-DRB1*1501 alleles in two sets of subjects (55). It is not certain whether the V α 8.1 association is functional, or the result of linkage disequilibrium with other genes in the region.

The TCR- δ locus also remains a candidate for this linkage. The function of TCR- $\gamma\delta$ cells is not known, but their location on mucosal surfaces, where allergens initiate IgE responses, may suggest a role in IgE regulation (56). Elucidation of the complex action of this locus awaits the construction of a comprehensive genetic and disequilibrium map of the region.

Genes influencing bronchial tone or responsiveness

The β_2 -adrenoceptor (β_2 -AR) is located on 5q32. It is the target of β_2 -agonists, which are widely used to treat asthmatic bronchoconstriction. It is expressed on pulmonary mast cells and bronchial smooth-muscle cells. Nine point mutations have been described within the β_2 -AR gene, four of which result in amino-acid substitutions; Arg16 to Gly, Gln27 to Glu, Val34 to Met, and Thr164 to Ile (57). These polymorphisms were not found to be more common in asthmatics than controls. However, Gly16 was more frequent in asthmatics that were steroid dependent or had been treated with immunotherapy. Gly16 has also been found to be more frequent than expected in asthmatics with nocturnal disease than other asthmatics (58). Subsequent studies have shown that Gly16 homozygotes had a greater loss of bronchodilator response after chronic β_2 -agonist treatment than Arg16 homozygotes (59). These associations may be explained by the increased agonist-mediated downregulation of β_2 -AR demonstrated by *in vitro* studies (60). The Glu27 polymorphism has been associated with reduced bronchial responsiveness (61).

Genes influencing non-IgE-mediated inflammation

Airway inflammation is a characteristic of asthma which may be independent of mechanisms controlling

atopy. Tumour necrosis factor-alpha (TNF- α) is a potent proinflammatory cytokine. It shows constitutional variations in its level of secretion which are linked to polymorphisms in the TNF gene complex (62–64). We have found that asthma was significantly increased in subjects with alleles associated with increased secretion of TNF- α , most notably the TNF- α promoter polymorphism TNF- α -308. When unrelated subjects only (the parents) were considered, the odds ratio for asthma in subjects homozygous for the high-secretor allele was 3.9 compared to homozygotes for the low-secretor alleles (65).

Whole genome screens for atopy and asthma

The genes and genetic linkages described above do not account for all asthma or atopy. To identify systematically genes predisposing to asthma, our group have carried out a complete genome screen in 80 nuclear families, with 300 markers spaced at approximately 10% recombination (66). We searched for linkage to one qualitative and four quantitative traits associated with asthma; namely, atopy, a skin prick test index, total serum IgE, the peripheral eosinophil count, and bronchial responsiveness. Six potential linkages ($P < 0.001$) were identified on chromosomes 4, 6, 7, 11, 13, and 16, five of which were to quantitative traits. Monte Carlo simulations showed that 1.6 false-positive linkages at this level of significance would be expected from the data. Two linkages, one to chromosome 11q13 and the other to chromosome 6 near the MHC, had been established previously. Three of the new loci (on chromosomes 4, 13, and 16) showed evidence of linkage to a second panel of families, in which maternal effects and pleiotropy of linked phenotypes were seen. The results showed the extent and the complexity of the genetic predisposition to asthma.

The American Collaborative Study on the Genetics of Asthma (CSGA) has also published the results of a genome-wide search in three different ethnic groups (67). Linkage was suggested on chromosomes 5q23–31, 6p21.3–23, 11p15, 12q14–24.2, 13q21.3, 14q11.2–13, and 19q13, in Caucasian sib pairs; on 5p15 and 17p11.1–q11.2 in African-American sib pairs; and on 2q33, 12q14–24.2, and 21q21 in Hispanic sib pairs. The level of significance for reporting potential linkages was not stringent ($P < 0.01$), so that some of the linkages will prove to be false positive. The results of a larger study by the same group are eagerly awaited.

Conclusions

The studies described in this review have demonstrated many possible loci linked to asthma and its

associated traits. The actions of several loci have been replicated in various studies, including those on chromosomes 5q (IL4/IL5 cytokine cluster), 6p (HLA and TNF), 11q (Fc ϵ RI- β), 12q, 13q, and 14q (TCR- α). The genetic basis of asthma and atopy is gradually becoming more certain; the methodological tools for finding genetic linkage and association are now established, and it is likely that all the important genes and their variants will be found in the next 5 years.

References

- Moffatt MF, Sharp PA, Faux JA, Young RP, Cookson WOCM, Hopkin JM. Factors confounding genetic linkage between atopy and chromosome 11q. *Clin Exp Allergy* 1992;22:1046-51.
- Cookson WOCM, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989;1:1292-5.
- Marsh DG, Meyers DA. A major gene for allergy – fact or fancy? *Nat Genet* 1992;2:252-4.
- Young RP, Lynch J, Sharp PA, Faux JA, Cookson WOCM, Hopkin JM. Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13. *J Med Genet* 1992;29:236-8.
- Shirakawa T, Morimoto K, Hashimoto T, Furuyama J, Yamamoto M, Takai S. Linkage between severe atopy and chromosome 11q in Japanese families. *Clin Genet* 1994;46:125-9.
- Collée JM, ten Kate LP, de Vries HG, et al. Allele sharing on chromosome 11q13 in sibs with asthma and atopy. *Lancet* 1993;342:936.
- Herwerden L, Harrap SB, Wong ZYH, et al. Linkage of high affinity receptor gene with bronchial hyperreactivity, even in absence of atopy. *Lancet* 1995;346:1262-5.
- Fölster-Holst R, Moises HW, Yang L, Fritsch W, Weissenbach J, Christophers E. Linkage between atopy and the IgE high-affinity receptor gene at 11q13 in atopic dermatitis families. *Hum Genet* 1998;102:236-9.
- Cookson WOCM, Young RP, Sandford AJ, et al. Maternal inheritance of atopic IgE responsiveness on chromosome 11q. *Lancet* 1992;340:381-4.
- Sandford AJ, Shirakawa T, Moffatt MF, et al. Localisation of atopy and the β subunit of the high affinity IgE receptor (Fc ϵ RI) on chromosome 11q. *Lancet* 1993;341:332-4.
- Sandford AJ, Moffatt MF, Daniels SE, et al. A genetic map of chromosome 11q, including the atopy locus. *Eur J Hum Genet* 1995;3:188-94.
- Shirakawa TS, Li A, Dubowitz M, et al. Association between atopy and variants of the β subunit of the high-affinity immunoglobulin E receptor. *Nat Genet* 1994;7:125-9.
- Hill MR, James AL, Faux JA, et al. Fc ϵ RI- β polymorphism and risk of atopy in a general population sample. *BMJ* 1995;311:776-9.
- Adra CN, Lelias J-M, Kobayashi H, et al. Cloning of the cDNA for a haemopoietic cell-specific protein related to CD20 and the beta subunit of the high-affinity IgE receptor: evidence for a family of proteins with four membrane spanning regions. *Proc Natl Acad Sci U S A* 1994;91:10178-82.
- Hill MR, Cookson WOCM. A new variant of the β subunit of the high-affinity receptor for immunoglobulin E (Fc ϵ RI- β E237G): associations with measures of atopy and bronchial hyperresponsiveness. *Hum Mol Genet* 1996;5:959-62.
- Shirakawa TS, Mao XQ, Sasaki S, et al. Association between atopic asthma and a coding variant of Fc ϵ RI- β in a Japanese population. *Hum Mol Genet* 1996;5:2068.
- Cox HE, Moffatt MF, Faux JA, et al. Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 1998;138:182-7.
- Marsh DG, Neely JD, Breazeale DR, et al. Linkage analysis of IL4 and other chromosome 5q31.1 markers and total serum IgE concentrations. *Science* 1994;264:1152-5.
- Meyers DA, Postma DS, Panhuysen CIM, et al. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5. *Genomics* 1994;23:464-70.
- Postma SD, Bleeker ER, Amelung PJ, et al. Genetic susceptibility to asthma – bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 1995;333:894-900.
- Amelung PG, Bleeker ER, Postma DS, et al. A locus regulating bronchial responsiveness maps to 5q. *Am J Respir Crit Care Med* 1995;151:A341.
- Panhuysen CIM, Xu J, Amelung PA, et al. Evidence for two loci regulating total IgE levels. *Am J Respir Crit Care Med* 1995;151:A341.
- Doull IJM, Lawrence S, Watson M, et al. Allelic association of gene markers on chromosomes 5q and 11q with atopy and bronchial responsiveness. *Am J Respir Crit Care Med* 1996;153:1280-4.
- Walley AJ, Bhattacharyya S, Leaves N, Daniels SE, Cookson WOCM. Linkage and allelic association of chromosome 5 microsatellite markers with atopic asthma phenotypes in a general population sample. *Am J Respir Crit Care Med* 1997;155:A257.
- Rosenwasser LJ, Klemm DJ, Dresback JK, et al. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. *Clin Exp Allergy* 1995;25 Suppl 2:74-8.
- Walley AJ, Cookson WOCM. Investigation of an interleukin promoter polymorphism for associations with asthma and atopy. *J Med Genet* 1996;33:689-92.
- Barnes KC, Neely JD, Duffy DL, et al. Linkage of asthma and total serum IgE concentration to markers on chromosome 12q: evidence from Afro-Caribbean and Caucasian populations. *Genomics* 1996;37:41-50.
- Nickel R, Wahn U, Hizawa N, et al. Evidence for linkage of chromosome 12q15-q24.1 markers to high total serum IgE concentrations in children of the German multicenter allergy study. *Genomics* 1997;46:159-62.
- Hershey GK, Friedrich MF, Esswein 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;337:1720-5.
- Deichmann KA, Heinzmann A, Forster J, et al. Linkage and allelic association of atopy and markers flanking the IL4-receptor gene. *Clin Exp Allergy* 1998;2:151-5.
- Sears MR, Herbison GP, Holdaway MD, et al. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Allergy* 1989;18:419-24.
- Levine BB, Stember RH, Fontino M. Ragweed hay fever: genetic control and linkage to HL-A haplotypes. *Science* 1972;178:1201-3.
- Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981;305:1551-9.
- Blumenthal MN, Awdeh Z, Alper C, Yunis E. Ra5 immune responses, HLA antigens and clonotypes [Abstract]. *J Allergy Clin Immunol* 1985;75:155.
- Freidhoff LR, Ehrlich-Kautzky E, Meyers DA, Ansari AA, Bias WB, Marsh DG. Association of HLA-DR3 with human immune response to *Lol p I* and *Lol p II* allergens in allergic subjects. *Tissue Antigens* 1988;31:211-19.

36. Ansari AA, Freidhoff LR, Meyers DA, Bias WB, Marsh DG. Human immune responsiveness to *Lolium perenne* pollen allergen *Lol p* III (rye III) is associated with HLA-DR3 and DR5. *Hum Immunol* 1989;25:59-71 (erratum 26:149).
37. Sriramarao P, Selvakumar B, Damodaran C, Rao BS, Prakash O, Rao PV. Immediate hypersensitivity to *Parthenium hysterophorus*. I. Association of HLA antigens and *Parthenium* rhinitis. *Clin Exp Allergy* 1990;20:555-60.
38. Fischer GF, Pickl WF, Fae I, et al. Association between IgE response against *Bet v* I, the major allergen of birch pollen, and HLA-DRB alleles. *Hum Immunol* 1992;33:259-65.
39. Marsh DG, Freidhoff LR, Ehrlich-Kautzky E, Bias WB, Roebber M. Immune responsiveness to *Ambrosia artemisiifolia* (short ragweed) pollen allergen *Amb a* VI (Ra6) is associated with HLA-DR5 in allergic humans. *Immunogenetics* 1987;26:230-6.
40. Reid MJ, Nish WA, Whisman BA, et al. HLA-DR4-associated nonresponsiveness to mountain cedar allergen. *J Allergy Clin Immunol* 1992;89:593-8.
41. Lympay P, Kemeny DM, Welsh KI, Lee TH. An HLA-associated nonresponsiveness to mellitin: a component of bee venom. *J Allergy Clin Immunol* 1990;86:160-70.
42. Sasazuki T, Nishimura Y, Muto M, Ohta N. HLA-linked genes controlling immune response and disease susceptibility. *Immunol Rev* 1983;70:51-75.
43. Young RP, Dekker JW, Wordworth BP, et al. HLA-DR and HLA-DP genotypes and immunoglobulin E responses to common major allergens. *Clin Exp Allergy* 1994;24:431-9.
44. Dekker JW, Nizankowska E, Schmitz-Schumann M, et al. Aspirin-induced asthma and HLA-DRB1 and HLA-DPB1 genotypes. *Clin Exp Allergy* 1997;27:574-7.
45. Loveridge JA, Rosenberg WMC, Kirkwood TBL, Bell JI. The genetic contribution to human T-cell receptor repertoire. *Immunology* 1991;74:246-50.
46. Moss PAH, Rosenberg WMC, Zintzaras E, Bell JI. Characterization of the human T cell receptor α -chain repertoire and demonstration of a genetic influence on V α usage. *Eur J Immunol* 1993;23:1153-9.
47. Gulwani-Akolar B, Posnett DN, Janson CH, et al. T cell receptor V-segment frequencies in peripheral blood T cells correlate with human leukocyte antigen type. *J Exp Med* 1991;174:1139-46.
48. Robinson MA. Usage of human T-cell receptor V beta, J beta, C beta and V alpha gene segments is not proportional to gene number. *Hum Immunol* 1992;35:60-7.
49. Moffatt MF, Hill MR, Corn  lis F, et al. Genetic linkage of the TCR- α/δ region to specific immunoglobulin E responses. *Lancet* 1994;343:1597-1600.
50. Robinson MA, Kindt TJ. Genetic recombination within the human T-cell receptor alpha-chain complex. *Proc Natl Acad Sci U S A* 1987;84:9089-93.
51. Corn  lis F, Hashimoto L, Loveridge J, et al. Identification of a CA repeat at the TCRA locus using yeast artificial chromosomes: a general method for generating highly polymorphic markers at chosen loci. *Genomics* 1992;13:820-5.
52. Boysen C, Carlson C, Hood E, Hood L, Nickerson DA. Identifying DNA polymorphisms in human TCR A/D variable genes by direct sequencing of PCR products. *Immunogenetics* 1996;44:121-7.
53. Heinzel FP, Sadick MD, Mutha SS, Locksley RM. Production of interferon gamma, interleukin 2, interleukin 4, and interleukin 10 by CD4+ lymphocytes *in vivo* during healing and progressive murine leishmaniasis. *Proc Natl Acad Sci U S A* 1991;88:7011-15.
54. Mohapatra SS, Mohapatra S, Yang M, et al. Molecular basis of cross-reactivity among allergen-specific human T cells. T-cell receptor V α gene usage and epitope structure. *Immunology* 1994;81:15-20.
55. Moffatt MF, Schou C, Faux JA, Cookson WOCM. Germline TCR-A restriction of immunoglobulin E responses to allergen. *Immunogenetics* 1997;46:226-30.
56. Holt PG, McMenamin C. IgE and mucosal immunity: studies on the role of intraepithelial Ia+ dendritic cells and δ/γ T-lymphocytes in regulation of T-cell activation in the lung. *Clin Exp Allergy* 1991;21 Suppl:148-52.
57. Reihsaus E, Innis M, MacIntyre N, Liggett SB. Mutations in the gene encoding the β_2 -adrenergic receptor in normal and asthmatic subjects. *Am J Respir Cell Mol Biol* 1993;8:334-9.
58. Turki J, Pak J, Green SA, Martin RJ, Liggett SB. Genetic polymorphisms of the β_2 -adrenergic receptor in nocturnal and nonnocturnal asthma. *J Clin Invest* 1995;95:1635-41.
59. Holgate ST. Asthma genetics: waiting to inhale. *Nat Genet* 1997;15:227-9.
60. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human β_2 -adrenergic receptor impart distinct agonist-promoted regulatory properties. *Biochemistry* 1994;33:9414-19.
61. Hall IP, Wheatley A, Wilding P, Liggett SB. Association of Glu 27 β_2 -adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects. *Lancet* 1995;345:1213-14.
62. Jacob CO, Fronck Z, Lewis GD, Koo M, Hansen JA, McDevitt HO. Heritable major histocompatibility complex class II-associated differences in production of tumor necrosis factor α : relevance to genetic predisposition to systemic lupus erythematosus. *Proc Natl Acad Sci U S A* 1990;87:1233-7.
63. Messer G, Spengler U, Jung MC, et al. Polymorphic structure of the tumor necrosis factor (TNF) locus: an NcoI polymorphism in the first intron of the human TNF- β gene correlates with a variant amino acid in position 26 and a reduced level of TNF- β production. *J Exp Med* 1991;173:209-19.
64. Wilson AG, Symons JA, McDowell TL, di Giovine FS, Duff GW. Effects of a tumour necrosis factor (TNF- α) promoter base transition on transcriptional activity [Abstract]. *Br J Rheumatol* 1994;33:89.
65. Moffatt MF, Cookson WOCM. Tumour necrosis factor haplotypes and asthma. *Hum Mol Genet* 1997;6:551-4.
66. Daniels SE, Bhattacharyya S, James A, et al. A genome-wide search for quantitative trait loci underlying asthma. *Nature* 1996;383:247-50.
67. Collaborative Study on the Genetics of Asthma (CSGA). A genome-wide search for asthma susceptibility loci in ethnically diverse populations. *Nat Genet* 1997;15:389-92.