

Genetics of asthma and allergic disease

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Atopic (allergic) asthma is the most common disease of childhood and is strongly genetic in origin. Many genome-wide screens for asthma and its associated traits have now been carried out, and genetic linkage has been consistently identified in several regions. It is probable that these loci contain major genes influencing atopy and asthma. Candidate genes have already been identified from the cytokine cluster on chromosome 5 and the MHC on chromosome 6. These complex regions contain more than one susceptibility locus for allergic disease. Other regions do not contain obvious candidate genes, and positional cloning of these loci is likely to identify novel disease pathways. Parent-of-origin effects are prominent at some of the loci and some also show linkage to other inflammatory immune diseases. Several single gene disorders are associated with allergic disease and on occasion are also linked to the same chromosomal regions. The positional cloning of asthma genes is now feasible.

INTRODUCTION

Asthma has become an epidemic, affecting 155 million individuals in the world. One child in seven in the UK wheezes (1) and similar numbers suffer from the related disorder of eczema (atopic dermatitis) (2,3). Asthma is due to a combination of strong genetic and environmental factors. It has risen in prevalence over the past 30 years in all Westernized societies (4), perhaps as result of loss of childhood infections (5–7). Asthma costs ~£1 billion a year to treat in the UK (8) and the pharmaceutical industry world-wide makes ~\$15 billion a year from drugs to treat the disease. The cost of treating eczema in the UK is also substantial, amounting to £0.5 billion each year (9). In children and young adults asthma is usually accompanied by allergic (atopic) phenomena such as elevation of the total serum immunoglobulin E concentration.

Many candidate gene and positional cloning studies of asthma have now been carried out. Although the number of candidate genes studies in asthma is growing rapidly, many contain small numbers of subjects and give equivocal results which do not subsequently replicate. This review will therefore concentrate on regions identified consistently through genetic linkage, because these by and large represent the strongest genetic effects, and candidates studied within these regions will be discussed in detail.

GENOME SCREENS

The first genome-wide screen for linkage to quantitative traits underlying asthma identified significant evidence for linkage on chromosomes 4q, 6 [near the major histocompatibility complex (MHC)], 7, 11q (containing *FcεRI-β*), 13q and 16 (10). A replication sample of families in the same study confirmed linkage to chromosomes 4, 11, 13 and 16 (10). A two-stage

screen in Hutterite families from the USA found suggestive evidence for linkage and replication for loci on chromosomes 5q, 12q, 19q and 21q (11). A screen in German families identified suggestive evidence for linkage to asthma on chromosomes 2q [near the interleukin-1 (IL-1) cluster], 6p (near the MHC), 9 and 12q (12). A genome screen for responsiveness to house dust mite allergen found suggestive linkage to chromosomes 2q, 6p (near the MHC) and 13q, as well as chromosome 8p (13). A genome screen in American families from three racial groups found weak linkage to broad regions that might match other studies on chromosomes 2q, 5q, 6p, 12q, 13q and 14q (14). A two-stage genome screen in French families found replicated linkage on chromosomes 1p, 12q and 17q (15). Thus, the loci most consistently and robustly identified by these screens are on chromosomes 5, 6, 12 and 13.

CHROMOSOME 5

Chromosome 5q31 has been studied by many groups, following an original observation of genetic linkage to total serum IgE concentrations in extended Amish pedigrees (16) and the confirmation of linkage to the same region (17). The region has also been linked to eosinophil levels (18) and to schistosomiasis resistance (19). The region contains several genes that modulate atopic responses, including those encoding IL-4, IL-13, IL-5, CD14 and GM-CSF.

Humans (and different strains of mice) seem to exhibit a constitutional preference for either cellular or humoral immune responses (5,20), which are associated with distinct cytokine profiles in helper T cells. The profiles are classified as Th₁ or Th₂ responses, respectively. Th₂ responses are characterized by high levels of secretion of IL-4, -13 and -5 and are associated with atopy.

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A number of polymorphisms have been identified in IL-13 and are convincingly associated with variation in IgE levels in large population samples (21). IL-13 enhances bronchial mucus secretion as well as up-regulating IgE production (22). It is in close proximity to IL-4 and is highly homologous to that gene. Polymorphisms within IL-4 have been less securely related to IgE levels or atopic disease than those within IL-13 (23,24). Functionally important polymorphisms within the IL-4 receptor α gene (on chromosome 16) associate with atopy and asthma (25,26), although positive findings are not universal (27).

CD14 is found on the surface of monocytes and macrophages, as well as in a soluble form (sCD14). CD14 acts as a high affinity ligand for bacterial LPS (endotoxin) and initiates the non-specific innate immune response to bacterial infection. A polymorphism upstream of the transcription start site for CD14 is associated with high levels of sCD14 and low levels of IgE (28). The prevalence of asthma correlates inversely with a rural lifestyle and high ambient levels of LPS, so it has been suggested that the CD14 interaction with LPS may be protective against allergic disease (28).

The level of variation in IgE associated with any of the chromosome 5 polymorphisms is of the order of 1–2% and the polymorphisms so far identified cannot be considered to have major influences on the allergic process. Genetic linkage maps of the region suggest the presence of at least two genes influencing atopy (29). Localizations within the region have been imprecise and the overall impression is that of a weak linkage to a number of adjoining loci.

However, the coincidence of non-homologous cytokine genes within a limited interval suggests that the region is involved in co-ordinate regulation of cytokine responses. Sequence comparison between human and mouse of 1 Mb of the proximal cluster, including IL-4, -13 and -5, found 90 non-coding highly conserved sequences (30). Fifteen of these elements were found to be present in other mammals (30). Characterization of the largest element in yeast artificial chromosome transgenic mice revealed it to be a coordinate regulator of IL-4, -13 and -5 (31). This work therefore has begun to unpick at a structural level the mechanisms for T cell commitment to a particular cytokine profile. It has also identified a high level of conservation of controlling elements of gene expression between species. It will be of interest to see whether this level of conservation is seen in other genomic regions.

CHROMOSOME 6

The MHC region on chromosome 6 has shown consistent linkage to asthma-associated phenotypes in several studies (10–14) and may be considered to be a major locus influencing allergic diseases.

The MHC contains many molecules involved in innate and specific immunity. At the same time, the asthma phenotype is complex, containing inflammatory and allergic components. Investigation of the effects of the MHC on asthma and its related phenotypes therefore poses a methodological and statistical challenge.

The class II genes of the MHC have recognized influences on the ability to respond to particular allergens (32–37). Asthma and bronchial hyper-responsiveness are associated

primarily with allergy to house dust mite and to a lesser degree with allergy to cat dander and moulds (38,39), so that genetic control of specific IgE responses is of relevance to clinical disease. The T cell receptor (TCR) genes, on chromosomes 7q and 14q, are also important potential genetic modifiers of the specific IgE response. Genetic linkage and allelic association has been reported between specific IgE responses and the TCR α/δ locus on chromosome 14q (40,41).

The class I genes of the MHC may have important effects on atopic responses, but these have not yet been adequately investigated. Similarly the class III complement genes contain polymorphisms which may be of relevance to inflammatory or immune diseases. These polymorphisms have not yet been tested in asthmatic subjects.

Non-classical MHC genes may also impact on asthma through non-allergic pathways and polymorphism in the control elements of inflammatory cytokines and their receptors is an important mechanism for flexibility in the immunoregulatory machinery (42). Tumour necrosis factor (TNF) is a potent pro-inflammatory cytokine which is found in excess in asthmatic airways. Polymorphism in the TNF complex is associated with variation in the expression of TNF- α and in the presence of asthma (43–45). These results emphasize the inflammatory nature of the asthmatic response, as distinct from its allergic basis.

CHROMOSOME 11q

Linkage of atopy to a variable number of tandem repeats on chromosome 11q13 was first reported in 1989 (46) and was at first disputed (47). The β chain of the high affinity receptor for IgE (Fc ϵ RI- β) was subsequently localized to the region. The Fc ϵ RI receptor acts as the allergic trigger on mast and other cells and is central to the allergic response (48). The β chain is not essential for Fc ϵ RI function, but both stabilizes the surface expression of the receptor and acts as an amplifying element within it (49). Any variation in the level of the β chain expression may therefore modify receptor function.

Polymorphism in Fc ϵ RI- β has been related to atopy (50), asthma (51), bronchial hyper-responsiveness (52,53) and severe atopic dermatitis (54). Polymorphism within the gene has also been associated with levels of IgE in heavily parasitized Australian aborigines, implying a protective role for the gene in helminth infestation (55).

Although coding changes have been identified within Fc ϵ RI- β (56,57), they are conservative and do not seem to alter gene function (58). The Ile181Leu polymorphisms identified by Shirakawa *et al.* (56) have not been found in several other studies (59–61), but have been found in association with asthma in Kuwaiti Arabs (62) and black South Africans (63). The difficulty in their identification nevertheless suggests that they are artefactual or in homologous sequences of the Fc ϵ RI- β gene. The structural variation causing the effects of this gene on asthma have therefore not yet been identified.

Genetic linkage and association of atopy to the locus have both been typified by a strong maternal effect (54,64,65), with preferential linkage and transmission of maternal alleles to affected children. Maternal effects are well recognized in allergic disorders and asthma, eczema, elevated serum IgE concentrations and skin prick test positivity in children have all been accompanied by an increased prevalence of asthma or

atopy in mothers (66). Preferential transmission of, or linkage to, alleles from either maternal or paternal sides has also been seen for other loci influencing allergic disease, including those identified on chromosomes 13 and 16 (10).

Parent-of-origin effects have been noted in other immunological disorders, including type I diabetes (67), rheumatoid arthritis (68), inflammatory bowel disease (69) and selective IgA deficiency (70). Parent-of-origin linkages have also been observed in the same diseases, so that preferential linkage of paternal alleles is seen from the insulin locus and type I diabetes (71) and HLA alleles for selective IgA deficiency (70). These findings suggest a common underlying mechanism for parent of origin effects in immune disorders. Monoallelic expression of cytokines and cell-signalling molecules is recognized (72–74) and mediated by methylation (75), providing a potential mechanism for these effects.

CHROMOSOME 12

The initial demonstration of genetic linkage of asthma to chromosome 12q (76) was followed by single-locus confirmatory studies (77,78) and by several general genome screens (11–15). In addition, a genome screen in a mouse model of asthma found linkage to bronchial hyper-responsiveness on mouse chromosome 10 in the region of syntenic homology to human 12q (79). The facility with which many groups have identified linkage to this region suggests that it is a true major atopy locus. *IFN- γ* does not seem to be responsible for the linkage. High density mapping of the region has been begun (80) and it is likely that positional cloning of the gene will be possible.

CHROMOSOME 13q14

Linkage of the total serum IgE to the esterase D (ESD) protein polymorphism on chromosome 13q14 was reported in 1985 (81). Linkage of chromosome 13q to atopy was confirmed by a genome-wide scan (10) and by a single locus study of Japanese families (82). The same study identified potential linkage disequilibrium between disease and *D13S153* (82). A two-stage screen in Hutterite families from the USA found linkage of asthma to 13q21.3 (11) in the first stage families but not in the second. Linkage to 13q14 has also been observed to house dust mite allergy in children with asthma (83) and to children with atopic dermatitis (84).

These results suggest that chromosome 13q14 also contains a major atopy locus. The same chromosomal region has been shown to be linked to total serum IgA concentrations (85). Low levels of serum IgA occur much more frequently in atopic children compared with normals (86) and salivary IgA deficiency is more common in infants with atopic parents (87). Immunoglobulin production is known to be under the control of many genes (reviewed in ref. 88), none of which have been mapped to chromosome 13q14. The gene of interest may encode a regulatory component of the humoral immune system, but alternatively, might influence both IgA levels and atopic status by influencing mucosal handling of allergens.

SHARING OF LOCI WITH OTHER DISORDERS

Genetic studies of other disorders may also have an impact on asthma and atopy. Crohn's disease and ulcerative colitis are

inflammatory bowel diseases of unknown aetiology which show familial clustering (89–91). Genome-wide screens have implicated loci on chromosomes 3, 7, 12 and 16 (92–94). The regions on chromosomes 7 and 12 may coincide with the asthma and atopy loci on the same chromosomes. Polymorphism in the *IL1* cluster on chromosome 2 has also been shown to influence the severity of the disease (95,96). A genome-wide screen in families with rheumatoid arthritis has similarly shown linkage near the asthma locus on chromosome 2 and the *TCR- α* locus on chromosome 14 (97). Linkage to type I diabetes is found near *Fc ϵ RI- β* on chromosome 11q13 (98). These findings suggest that important genes or gene families may be common to several inflammatory and immune disorders.

MENDELIAN DISORDERS

Asthma, eczema and allergic disease are associated with a number of Mendelian disorders. The identification of genes causing such disorders is much easier than the positional cloning of complex disease genes. These Mendelian disorders may therefore be extremely helpful in identifying genes influencing asthma and allergy. They include Netherton's syndrome (99,100), Job's syndrome (also known as hyper IgE syndrome or Buckley's syndrome) (101), thymic hypoplasia (DiGeorge syndrome), cellular deficiency with immunoglobulins (Nezelof syndrome) (102), selective IgA deficiency (87) and Wiskott–Aldrich syndrome.

Netherton's syndrome is a rare recessive disease in which children are born with a severe ichthyotic dermatosis (99). Severe symptomatic atopy is a universal accompaniment of the disease (100). The gene for Netherton's syndrome has recently been located distal to the chromosome 5 cytokine cluster (103) and the gene underlying the disorder has been identified as *SPINK5* (104). *SPINK5* codes a multi-domain serine protease inhibitor *LEKTI*, which is expressed in the epithelium, mucosa and thymus (105). Common coding polymorphisms have been identified in the gene by our group and these show associations with atopy, asthma and eczema in children without Netherton's syndrome. These findings therefore define a new pathway for allergic disorders.

Other Mendelian disorders localize to regions that may be relevant to common allergic disease. Selective IgA deficiency has been localized to the MHC (70). Hyper-eosinophilia syndrome has been localized to the distal part of the chromosome 5 cytokine cluster (106) and it is of interest that acquired hyper-eosinophilia is consistently associated with translocations on 5q35 (107,108). Hyper IgE syndrome has been linked to the distal arm of chromosome 4q (109). A small chromosomal deletion in one child with the disease may have limited this localization to a 20 Mb interval (109). Linkage of the total serum IgE to this region has been seen in at least one genome scan (<http://www.well.ox.ac.uk/asthma/public/GenomeScan/index.html>) (10), suggesting that this locus may also have an effect in normal regulation of IgE levels.

CONCLUSIONS

The positional cloning of genes underlying asthma and allergic disorders is becoming increasingly tractable. Agreed regions of strong genetic linkage have emerged, some of which coincide

with linkages to single gene disorders or to other immunological diseases. The completion of the human genomic sequence and the availability of deep public EST databases mean that laborious physical mapping of these loci may not be necessary. The key element in gene discovery will be the identification of robust patterns of linkage disequilibrium (LD) between markers and disease. LD mapping of at least one atopy locus has shown that LD is irregularly distributed (110) and the challenge is to develop statistical as well as genotyping methods to handle dense local single nucleotide polymorphism maps.

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