

Summary

Tarja Laitinen

Heredity of Allergy and Asthma

Asthma and other atopic disorders belong to a large group of common, multifactorial diseases. In these diseases the specific mechanisms of inheritance have been difficult to elucidate because of genetic heterogeneity between the patients and environmental factors that modify the expression of the disease. For studies estimating the proportion of genetic compared to environmental component in the development of these diseases, twins provide a unique setting, whereas family settings are needed when the mode of inheritance is studied. Over the years both family and twin studies have shown unambiguously a significant genetic component in the inheritance of atopic clinical conditions as well as in many atopy-associated quantitative traits, such as total and specific serum immunoglobulin E (IgE) level, blood eosinophil count, and bronchial hyperreactivity, even though the mode of inheritance and contributing genes have remained unknown. Obviously, the pattern of inheritance and the set of contributing genes can differ between the phenotypes. Genome-wide gene-mapping studies support the notion of multiple genes interacting to determine genetic susceptibility to asthma. On the other hand, within respective families, simultaneous occurrence of one to two loci with major influence on the development of the disease is enough to explain the increased risk observed among other family members. These loci act possibly with remarkably lowered penetrance and under the influence of individual genetic makeup (minor susceptibility and protective loci) and environmental disease modifying factors. Therefore, it is plausible that genetic heterogeneity can be found also among patients/families/ethnic groups expressing the same phenotype. The challenge of the future gene-mapping studies is especially to recognize the major loci that can give us the most valuable information of signaling pathways of importance in the pathogenesis of asthma. This chapter briefly summarizes the results of twin and family studies and the role of population selection in genetic studies. In addition, it represents two simplified models of inheritance of asthma that will help the reader to understand the underlying genetic mechanisms in the development of atopic disorders and to evaluate the power and the results of genetic studies.

Key Words: Asthma, atopic disorders, inheritance of complex traits, twin studies, family studies, founder populations.

Summary

Matthias Wjst

Genome Scans for Asthma

After summarizing basic principles of positional cloning in complex diseases, published genome scans for asthma and associated traits are discussed for both human and mice studies. A side-by-side comparison of the results reveals at least four linkage regions that are observed by the majority of the genome scans. Future strategies for finding the asthma genes in the linked regions are reviewed in the light of the current research.

Key Words: Microsatellite marker, positional cloning, linkage, genome scan, asthma, immunoglobulin E, bronchial hyperreactivity, allergy, human, mouse, SNP, sequencing.

Summary

Carole Ober

The role of founder populations in mapping complex disease genes: studies in the South Dakota Hutterites

Founder populations offer advantages for mapping complex trait genes because their relatively small ancestral gene pool decreases genetic heterogeneity and because their relatively recent ancestries increases the extent of linkage disequilibrium. The Hutterites are a young founder population that has been the subject of our genetic studies of asthma and atopy. A genome-wide screen revealed evidence for linkage to asthma or atopy in 16 chromosomal regions, 10 of which have been linked to asthma or a related phenotype in genome screens in other populations. These 10 regions likely contain susceptibility loci that are common variants present in diverse population and perhaps with relatively large effects on asthma or atopic phenotypes.

Key Words: Asthma, atopy, mapping, founder populations, genome-wide screen, Hutterites, linkage disequilibrium, linkage.

Summary

Nobuyuki Hizawa

Genetic regulation of specific IgE responsiveness

It is critical to identify susceptibility factors in the development of specific IgE responses toward common environmental allergens because of the impact that allergy has on public health. Genetic regulation of total IgE levels emerges as a strong determinant of specific IgE responses toward complex allergens in addition to genes encoding the HLA complex and the TCRs. This contention was recently supported by independent genome-wide linkage analyses, which identified several non-*HLA* regions, including 5q31-q33 and 11q13, responsible for the development of specific IgE responses. The actual contribution of these genetic components, including the relative importance of specific *versus* overall IgE regulation, remains obscure, and increasing evidence indicates a role for genetic heterogeneity and complex interactions between genetic and environmental components in the regulation of specific IgE responsiveness. Further studies will examine the presence of variants in a series of candidate genes with an emphasis on their functional outcomes to assess the complex gene-gene and gene-environment interactions.

Key Words: Specific IgE response, complex allergen, *dermatophagoides pteronyssinus*, HLA, TCR, 5q31-q33, 11q13, total IgE level, gene-gene interaction, gene-environment interaction, genetic heterogeneity.

Summary

Adel H. Mansur

Genetic variation at the HLA and TCR loci and the development of allergy and asthma

Studies of the genetic predisposition to atopy and asthma have focused on the important genetic influences that are exerted over the recognition of allergenic antigens and subsequent propagation of immune response involving T cells, B cells, and IgE synthesis. In particular, studies have focused on the Human leukocyte antigen (HLA) and T cell receptor (TCR) genes giving their central role in the handling and recognition of exogenous antigens.

Data from genome screens and candidate gene approach studies have provided unequivocal evidence for a role played by the HLA genes in the predisposition to the allergic diathesis. However, the strength of linkage between the HLA and allergy in genome screens was generally modest, implying an important non-HLA genetic component. Methodical difficulties at the early stages of research in this field resulted in inconsistency in terms of the HLA-types associated with the allergic diathesis. Lack of recognition of problems of reactivity to multiple allergens, presence of extended haplotypes and low-resolution molecular techniques applied in HLA typing, and the generally small size of populations studied all have contributed to the observed inconsistency between studies in this field. However, a large-body of literature is now becoming available that is producing interesting results. The association between the DRB1*15 and ragweed allergy is now well established. In addition, there is also good evidence to implicate other HLA alleles/haplotypes in either predisposition to or protection against general atopic status and asthma. The DRB1*07 has been associated with allergies to olive, birch tree pollens, as well as with citrus- and housedust-mites-induced asthma, nasal polypsis, allergic bronchopulmonary aspergillosis, high total serum immunoglobulin E (IgE), and the general atopic status. In contrast, the DQB1*0502 allele seems to confer protection against isocyanate-induced asthma, western red cedar-induced asthma, atopy, and specific allergies. There are many other claims of associations between different HLA alleles and the allergic diathesis that remain to be confirmed. The human HLA region has now been fully sequenced. In addition, there have been advances in the molecular techniques used in HLA-typing that provide typing results with ever-improved resolution and consistency. Having taken into account the early encountered problems in study design and methodology, we should be optimistic and expect to establish more precisely the role HLA genes in asthma and allergy.

Similarly, the TCR genes are attractive candidates that have been linked by genome screens and candidate-gene studies to the allergic diathesis. At the germline level, the TCR α/β heterodimer is encoded by the TCR A locus on chromosome 14q11.2 and the TCR B locus on 7q35. Current evidence suggests genetic linkage between the allergic diathesis and the TCR A locus, but the evidence for linkage with the TCR B locus remains weak. The TCR α/β molecule is expressed on the surface of mature and developing T-cells providing antigen specificity to each T-cell clone. The total population of T-cells with particular antigen specificity in any individual represents the T-cell repertoire that could be studied by analysing either the α or β chains of the TCR. The TCR α -chain repertoire might be under stronger genetic control, while the TCR β -chain repertoire is probably more varied and more influenced by environmental factors including super-antigens. Usage of particular TCR V gene families may induce the development of the Th2 subtype of T-cells, which promote IgE production. The identification of certain V genes in allergy may lead to characterisation of antigenic epitopes with the possibility of using these epitopes as peptides for immunotherapeutic purposes. Evidence for the presence of a restricted T-cell repertoire with oligoclonal expansion in atopy in response to specific antigen stimulation has been shown in synthetic conditions including *in vitro* stimulation, animal models, and human-based studies. In humans, there is evidence to suggest that the TCR repertoire is modulated with T cell

oligoclonality seen in both the bronchoalveolar fluid and peripheral blood of atopics and/or asthmatics, usually in response to specific allergen challenges. However, this was not universally reported in the so-far small number of studies published. In addition, there has been considerable technical limitation encountered in studying the repertoire. The number of available V family-specific monoclonal antibodies used to determine the repertoire was limited, giving suboptimal coverage of the repertoire, while the PCR-based techniques suffered from lack of consistency. Studies on the TCR repertoire will become more reliable as more antibodies against a wider range of V α and V β segments become available, as well as with the advent of more robust quantitative PCR-based methods.

HLA/TCR interaction in the modification of the immune response has been reported in both animal and human studies. In the B6 mouse, germline variation in particular TCR AV segments has been shown to have a major influence on MHC selection. In humans, one study showed that specific IgE to *Der p* II antigens of the house dust mite (HDM) was confined to subjects who were positive for TCR AV8S1*2 and HLA DRB1*1501, while a further study reported interaction between DRB1*0701 and a marker to TCR A/D leading to a significant increase in total serum IgE levels. This early data suggest that germline HLA/TCR interaction may play an important role in restricting the allergic responses and highlight the importance of the combined consideration of the HLA/TCR genes in studying the genetics of allergy. Finally, as shown in genome screens and candidate-gene studies, there are non-HLA/TCR loci that are important in asthma and allergy. A future aim should be to study the interaction of such genes with the HLA/TCR in properly designed studies that also should take into account the strong environmental modulating factors.

This chapter provides an overview of the molecular mechanism implicated in the initiation and propagation of the allergic response with a focus on the genetics of the HLA and TCR. Published studies addressing the role of HLA and TCR gene variation in asthma and allergy are reviewed.

Key Words: HLA, TCR, loci, polymorphism, variation, repertoire, allergy, asthma, IgE, specific responses.

Summary

C.N. Adra, X.-Q. Mao, A. Yamasaki, P.-S. Gao, Xing Yang, T. Shirakawa and J. M. Hopkin

Chromosome 11q13, Fc ϵ RI β and atopic asthma

Atopy characterized by increased general IgE responsiveness is an important cause of disorder in the skin (eczema), lungs (asthma) and nose (rhinitis), and is derived from genetic and environmental factors. The first genetic region reported to show linkage to atopy was chromosome 11q13 in a maternal line. Variants of the candidate gene, *FCER1B* mapped to chromosome 11q13.1 have been identified; three coding polymorphisms are Ile181Leu, Val183Leu and Glu237Gly. A strong association was seen between these variants and atopy and/or asthma phenotypes. A number of studies therefore implicate the *FCER1B* as the strongest candidate for atopy locus on 11q13.

Key Words: 11q13, Fc ϵ RI β , atopy, asthma, eczema, rhinitis, polymorphism, bronchial hyper-responsiveness, total IgE level, allergy.

Summary

Tineke C.T.M. van der Pouw Kraan, John W. Holloway, Lucien A. Aarden and Jaring S. van der Zee

Genetic regulation of Interleukin-13 production

In this chapter we review the critical and specific role of the effector molecule IL-13 in clinical and experimental asthma and COPD. Inhibition of IL-13 activity in the lungs of sensitized mice prevents several characteristics of asthma, whereas neutralization of IL-4 fails to do so. Pulmonary expression of transgenic IL-13 in adult mouse lungs results in a COPD phenotype with inflammation, mucus metaplasia and emphysema. In clinical asthma, an increased capacity of human bronchial T cells to produce the Th2 cytokines IL-4, IL-5 and IL-13 is observed. These findings strongly suggest a prominent role of IL-13 in human asthma and COPD as well and implicate IL-13 as a major therapeutic target in these diseases.

The IL-4, IL-5, and IL-13 genes are closely linked, IL-4 and IL-13 being separated by only 12.5 Kb and IL-5 by 150 Kb from IL-4 on chromosome 5q31, a region associated with AHR, atopy and asthma. This region contains several polymorphisms, including the IL-13 promoter polymorphism -1055 C to T, which is associated with increased binding of transcription factors, altered regulation of IL-13 production, and with allergic asthma and COPD.

Key Words: IL-13, IL-13 receptors, IL-4, Th2 cytokines, asthma, mucus production, airway remodeling, polymorphisms, T cell, cyclosporin A, stat-6, NF-AT, COPD.

Summary

Roy C. Levitt, Michael P. McLane, Luigi Grasso and Nicholas C. Nicolaides

The role of interleukin-9 and the interleukin-9 receptor gene candidates in asthma

Atopic asthma is a complex heritable disorder with clinical manifestations of airway hyperresponsiveness (AHR), eosinophilic inflammation of the lung, and elevated serum total IgEs. Recently, genetic linkage studies and functional genomics in humans and mice have implicated interleukin-9 (IL-9) and IL-9 receptor in the genetics of AHR allergy and asthma. Recent evidence supports a central role of IL-9 as a regulator of AHR and allergic asthma and mucosal TH2 immunity. In this chapter, genetic and functional studies that identify IL-9 and its receptor as key in the pathogenesis of asthma are reviewed. Evidence is presented from recombinant cytokine instillation and neutralizing antibody studies as well as overexpressing transgenic models that *in toto* support the thesis that IL-9 is both necessary and sufficient to produce all histomorphological and physiologic signs of asthma.

Key Words: Atopic asthma, airway hyperresponsiveness (AHR), eosinophilic inflammation, asthma, allergic asthma, mucosal TH2 immunity, chromosome 5q31-q33, genetic linkage, Interleukin-9, (IL-9), eosinophilia, quantitative trait locus (QTL), alpha chain of IgE receptor, IL-5R α , IL-9 transgenic mice, serum total IgEs, MUC2, MUC5AC, mast cells, rIL-9, bronchoalveolar lavage (BAL) eosinophils, FVB/N-TG5, allergens, RT-PCR, dust-mite antigen (DMA), TH2 mucosal immunity, IL-9 neutralizing antibody, long arm XY pseudo-autosomal region, IL-9 receptor, IL-9-specific blockade, neutralizing antibody.

Summary

Hartmut Grasemann and Jeffrey M. Drazen

Genetics of the nitric oxide synthetic pathway in asthma

Nitric oxide (NO) is enzymatically formed by nitric oxide synthases (NOSs). NO is involved in a number of physiological and pathophysiological processes within the airways that are important in conditions such as airway inflammation, allergic disease, and asthma. Multiple genetic studies in families have established linkage of chromosomal region 12q to allergic disease, increased serum IgE, and the diagnosis of asthma. The gene encoding for the neuronal form of NOS (NOS1), which has been localized to chromosomal region 12q, is an attractive asthma candidate gene for a number of reasons. Numerous experimental studies with both animals and humans indicate that neurogenic factors are important in asthma. NOS1 is important in asthma airway hyperreactivity since mice deficient for *nos1* are less responsive to airway challenge than are wild-type mice and *nos2*-deficient mice after allergen sensitization and challenge. Case-control studies have established an allelic association between polymorphic markers in the NOS1 gene and the diagnosis of asthma. Furthermore, airway NO concentrations are increased in patients with asthma and are associated with the size of an intronic NOS1 microsatellite.

Key Words: Nitric oxide, nitric oxide synthase, NOS1, NOS2, airway NO; airway responsiveness, genome-wide scans, case-control association studies.

Summary

I. Sayers and A.P. Sampson

Genetic regulation of leukotriene production and activity

Leukotrienes (LT) represent a family of lipid mediators that have a central role in the pathogenesis of asthma. Leukotrienes potently contract human bronchial smooth muscle, promote mucus secretion and impair muciliary clearance, increase vascular permeability leading to airway oedema, and specifically chemoattract human eosinophils *in vitro* and *in vivo*. In view of the importance of these lipid mediators, substantial effort has been directed at elucidating the mechanisms regulating their production by the 5-lipoxygenase pathway and those which mediate their effects.

This chapter reviews the current understanding of the role of the micro-environmental and genetic mechanisms in determining the production and activity of leukotriene mediators in asthma. A particular emphasis is placed on the role of genetic polymorphism in genes encoding enzymes involved in the production of leukotrienes as disease susceptibility or disease modification markers. The concept of genetic polymorphism in LT related genes determining the efficacy of LT modifier drugs in asthma is also described. These drugs are the first entirely new treatments for asthma in over 20 years, and a greater understanding of the role of genetic determinants in drug efficacy will promote the targeting of these compounds to patients who are most likely to benefit.

Key Words: Leukotrienes, asthma, 5-lipoxygenase pathway, CysLT1 and CysLT2 receptors, genetic polymorphism, asthma susceptibility, disease modification, pharmacogenetics.

Summary

Ladina Joos, Peter D. Paré and Andrew J. Sandford
Genetics of Asthma Severity

There is a major hereditary contribution to the etiology of asthma and allergic diseases. However, only a few epidemiological studies have examined whether there is a genetic contribution to asthma severity. Overall, there is little evidence for a strong genetic influence on asthma severity, although this could be related to lack of well-designed studies to test the heritability of severity. We discuss a variety of candidate genes that have been studied for their involvement in asthma severity. Different approaches to assess disease severity are reviewed.

Key Words: Asthma severity, genetics, polymorphisms, association studies, IL4, β 2-adrenergic receptor, TNF α , alpha-1-antitrypsin, platelet-activating factor acetylhydrolase, severity score.

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