Genetic Aspects of Atopy and Atopic Dermatitis

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SUMMARY This review presents updated evidence on the genetic basis of atopy and atopic dermatitis. The etiology of atopic processes remains partially unknown but is likely to result from multifactorial inheritance, with an interaction between genetic and environmental factors. It seems that at least two major mechanisms, non-antigen specific and antigen specific, regulate the immune response to environmental allergens in humans. While many of environmental components have been studied for years, only recently significant progress has been made in identifying the genes responsible for susceptibility or expression of atopic diseases. Genome-wide screens in various populations have identified the locations of susceptibility genes for asthma and atopy as well as associated phenotypes such as bronchial hyperresponsiveness and increased total IgE concentrations typical for patients suffering from atopic dermatitis. Further research on genetic and environmental relationships is necessary for better understanding of atopic processes and development of new therapeutic approaches.

KEY WORDS: atopy; atopic dermatitis; genetics; candidate genes; positional cloning

INTRODUCTION

Immunoglobulin E (IgE) is produced by all individuals as a defense against large quantities of antigens, e.g., during helminthic infestation. In contrast, IgE production against common antigens, such as house dust mite, is characteristic for atopy. Thus, atopy can be defined as an increased tendency to react to environmental agents by production of IgE antibodies. Atopic status can be manifested clinically as one or more of atopic disorders, which include atopic asthma, atopic dermatitis, allergic rhinitis and conjunctivitis. Atopic disorders form a group of different clinical phenotypes and therefore a complex pattern of inheritance is strongly suggested (1,2).

Atopic dermatitis (AD) is a chronic, inflammatory disease that usually starts in early infancy. It is characterized by eczematous, inflammatory skin lesions and severe xerosis. The prevalence of AD is approximately 20% in the general population, with an increasing tendency, especially in developed countries (3). According to Hanifin and Rajka, the major diagnostic features of AD include personal or family history of atopic disease, while among minor features there are also elevated serum total (tIgE) and antigen specific IgE (aslgE) concentrations (4). Approximately 80% of AD patients present high tIgE serum concentration that may correlate with the disease severity. However, in approximately 10%-20% of AD patients tIgE serum concentration stays within the normal range and no aslgE are detected (5). Usually first atopic skin lesions appear in early infancy and in 45%-50% of patients fade during the second year of life. In another 50%-65%, skin lesions persist or relapse after puberty. In about 40%-45% of cases, other atopic diseases may occur, especially atopic asthma (6).
PATHOGENESIS OF ATOPY

Immune dysfunction, particularly enhanced T-cell activation, plays a pivotal role in atopic processes. Exposure to various environmental allergens in an atopic individual results in IgE production by B cells. IgE antibodies are produced after presentation of an antigen fragment by antigen presenting cells (APC) and in close cooperation with T helper type 2 cells (Th2). IgE molecules are bound on the surface of mast cells and basophils via high-affinity receptors for Fc fragment of immunoglobulins type I (FcεRI). When IgE recognizes the allergen, a cascade of immune reactions begins. Mast cells and basophils release inflammatory mediators, such as cytokines. These cytokines influence the inflammatory reaction, IgE production (IL-13 and IL-4) and activate other inflammatory cells in terms of allergy reaction (IL-5, IL-8, IL-9). Th2 cells play a critical role in the regulation of IgE production. In an acute stage of inflammation in AD there is a predominance of Th2 cells, whereas in case of chronic skin lesions Th1 cells tend to predominate. It is well known that specific, complex cytokine pattern of the microenvironment determines this biphasic characteristics of inflammation in AD patients. It is also stressed that certain chemokines (chemotactic cytokines) may localize and enhance skin inflammation by inducing chemotaxis and activation of inflammatory cell types as well as sustaining Th2 response during the Th1-dominant phase of AD (7,8).

GENETIC BACKGROUND OF ATOPY

Because of the possible effects of many shared environmental factors, familial aggregation alone is not sufficient to verify the genetic basis of atopic diseases. Therefore, twin and family studies are required.

Twin studies compare disease concordance rates between monozygotic and dizygotic twins. The degree of reduction from 100% concordance in monozygotic twins reflects the degree to which environmental factors contribute to the disease. Twin studies support the role of genetics in atopic disorders but also indicate a possible role of environmental factors (9,10).

There are two main directions of studies on genes influencing atopy: searching for those genes responsible for increased total IgE levels and for a correlation between major histocompatibility complex (MHC) genes and specific IgE response to environmental allergens. The overall regulation of IgE is genetically determined. The genetic regulation of serum IgE was studied by Marsh et al. in the Pennsylvania Old Order Amish, a religious isolated group (11). The evidence for linkage with total IgE was found within the 5q31.1 region. Further studies have suggested that the gene coding IL-4 and nearby genes in the 5q31.1 regulate production of nonspecific IgE. Studies in families with asthma have revealed that a polymorphism in the IL-4 promoter is associated with elevated total serum IgE levels. An analysis of IL-4 gene expression identified a higher expression in individuals having T (thymine) variant at position 590 that those with C (cytosine) polymorphism. Another potential "atopy gene" is located in region 11q13 of chromosome 11. This region contains FCERIB gene of β chain high-affinity IgE receptor, which takes part in signal transduction and activation of mast cells and basophils. Polymorphism in positions 181 and 183 and the presence of leucine correlate with atopy (12).

Chromosomal region 12q14.3-q24.1, similar to chromosome 5q, is rich in candidate genes for atopy. This region contains genes for IFN-γ, which inhibits IL-4 and a gene for STAT6 protein, which is a transcription factor, transducing signal for Th2 cells differentiation (13). Region 16q21 is also a marker of atopy with a gene for IL-4 receptor. Mutation in position 1920 of subunit α IL-4R gene was observed in 70% of atopic individuals (14).

Table 1. Candidate genes and their chromosomal regions showing linkage to total IgE and atopy

<table>
<thead>
<tr>
<th>Candidate genes</th>
<th>Chromosomal regions</th>
<th>Function</th>
<th>References</th>
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<tbody>
<tr>
<td>IL4, IL13, IL5</td>
<td>5q31.1-q33</td>
<td>B-cell switching to IgE, Th2 response</td>
<td>[10,11]</td>
</tr>
<tr>
<td>β FcεRI</td>
<td>11q13</td>
<td>Transduction signaling on basophils, mast cells and dendritic cells</td>
<td>[12]</td>
</tr>
<tr>
<td>IFN-γ, STAT6</td>
<td>12q14.3-q24.1</td>
<td>Inhibits IL-4 activity, transcription factor</td>
<td>[13]</td>
</tr>
<tr>
<td>α IL-4R</td>
<td>16p21</td>
<td>IgE overproduction</td>
<td>[14]</td>
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The HLA-D region in chromosome 6p21.3 contains a group of candidate genes involved in antigen presentation. APC may present antigen to T cells which binds it via T-cell receptor (TCR) only in the presence of MHC class II molecule on the surface of APC (MHC class II restriction). Specific responsiveness to ragweed (Ambrosia artemisiafolia) allergens Amb a 5 (5 kDa) and Amb a 6 (9.9 kDa) was studied. The study showed a relationship between the presence of HLA Dw2 molecule with specific IgE and IgG antibody responsiveness to Amb a 5 allergen but not to larger Amb a 6 antigen, which is found in higher concentrations. Furthermore, HLA-DRβ1 residues were defined as being critical for the immune recognition of the major Amb a 5 epitope (15,16).

Over several years, numerous studies have confirmed these findings and associations with HLA-DR have been extended to several allergens, e.g., house dust mite Der p 1, Der p 2 (17,18). Tables 1 and 2 present candidate genes and their chromosomal regions, showing linkage to tIgE or asIgE and atopy.

<table>
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<tr>
<td>HLA-DR</td>
<td>6p21.3</td>
<td>Antigen presentation</td>
<td>[15]</td>
</tr>
<tr>
<td>TCR</td>
<td>14q11.2-13</td>
<td>Interacts with MHC complex</td>
<td>[16]</td>
</tr>
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**GENETICS OF ATOPIC DERMATITIS**

Twin studies of AD performed in 1989 by Larsen et al. revealed a coexistence in 72%-86% of monozygotic twins and in 21%-23% of dizygotic twin pairs, indicating a strong genetic background (19). Two genome screens for AD were undertaken in children. The first one was performed in 2000 by Lee et al. in families of German and Scandinavian children, and showed linkage to chromosome region 3q21 (20). The second screen of British families, performed in 2001 by Cookson et al., including children affected by AD, extended Lee’s research and revealed another three chromosomal regions of linkage to AD on chromosomes 1q21, 17q25 and 20p (21). The third genome screen carried out by Bardley et al. in Swedish adults with AD showed evidence for linkage of AD to chromosome region 3p24-22. The latter authors also found suggestive linkage to region 18q21, especially in AD, combined with raised allergen-specific IgE levels, and a connection between the severity of AD and regions 3q14, 13q14, 15q15-14, 17q21 (22). Interesting is the fact that the regions identified in the British 1q21, 17p25, 20p and the German 3q21 investigations closely correspond with the genes known to be psoriasis susceptibility genes (23). Genetic region 3q21 is also concerned with a predisposition to asthma, type 1 diabetes, and rheumatoid arthritis (24).

Candidate genes have also been studied for a role in AD. Polymorphism in the β chain of the high-affinity receptor for immunoglobulin E (FcεRI-β) has been screened in different studies on asthma, bronchial hyperresponsiveness, and severe atopic dermatitis (25-27). In the same way, a connection between polymorphism of mast cell tryptase (chymase) and AD was revealed in a Japanese population (28). However, these results have not been replicated in other studies (29). Allergic inflammation is characterized by overexpression of family C-C chemokines. A functional mutation in the promoter of the RANTES (regulated on activation, normal T cell expressed and secreted) gene has been identified and is associated with AD in children but not with asthma (30). Netherton’s disease is a rare, autosomal recessive skin disorder characterized by trichorrhexis invaginata, congenital ichthyotic erythroderma, and atopic diathesis. The Netherton’s gene has been localized to chromosome 5q31 near the interleukin-4 cytokine cluster and has been identified as SPINK5. SPINK5 gene encodes a 15-domain serine protease inhibitor LEKTI (lympho-epithelial Kazal-type-related inhibitor), which is expressed in the thymus. Recently, coding polymorphism in SPINK5 gene (a variant with lysine instead of glutamine at position 420) has been reported to be associated with atopy, asthma and AD. The gene is expressed in the outer layers of the skin and may play a protective role against allergens which are serine proteinases (31). Animal models are often helpful in identifying genes involved in disease. The NC mouse model spontaneously develops AD-like skin lesions and elevation of total IgE serum levels. A genetic study of this model revealed linkage to chromosome 9, which is homologous to human chromosome 11q23 (32). Another mouse model of AD is NOA mouse (The Naruto Research Institute Otsuka Atichia). Here linkage has been...
established in region on chromosomes 13 and 14, which are homologous to human locus on 13q14 and 5q31, respectively (33).

Many genome screens have been carried out for asthma. Regions of linkage to atopy have been identified on chromosomes 5q35, 11q13, 12q, 14q, 16q and 6p (see Tables 1 and 2). What seems interesting is that regions thought to be linked to AD did not totally correspond to those loci. This is suggestive of a presence of separate or additional genes that may act through atopic mechanisms (23).

Numerous studies are carried out in many world centers and methods of molecular genetic mapping of genes are becoming ever better. Nevertheless, the “atopy gene” has not yet been identified. Until now, only some of the genes responsible for separate parts of the allergic reaction chain have been determined. As far as the genetic background of any disease is concerned, the influence of environmental factors is a sine qua non condition, which, however, is a very difficult task.

References


Nivea cream is the only cream containing eucerite.
From the Nivea collection of Zlatko Puntijar (1933)