secretory granules of mast cells.

List of original publications

In addition, this thesis includes the results concerning tryptase and chymase activity in skin blisters induced by freezing with liquid nitrogen published in Table I of the following article:

Genetic Studies of Atopic Dermatitis
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A marked increase in the prevalence of atopic dermatitis (AD) and other atopic diseases (allergic asthma and allergic rhinoconjunctivitis) has been reported during the past few decades. In Sweden the prevalence of AD in schoolchildren more than doubled between 1979 and 1991, and may now be one of the highest in the world, approximately 15%. AD is considered to be a multifactorial disorder caused by both genetic and environmental factors, although the relative contributions of genes and environment are unknown. Multifactorial disorders are characterized by lack of Mendelian inheritance patterns, and the phenotypic expression is probably modified by the genotype of several loci and environmental factors. When evaluating the genetic contribution of these disorders, several lines of evidence are important, such as familial aggregation, twin studies and migration/adoption studies. Twin studies in AD support the role of a strong genetic contribution with a concordance rate of 0.86 in monozygotic twins and 0.21 in dizygotic twins. When both parents have AD, children have a risk of up to 75% to develop the disease.

One way to reveal the etiology of a complex human disease with an inherited component is to identify genes contributing to the disease. This can be done with different strategies. Random genomic screening involves testing the phenotype for linkage by scanning the entire human genome with a large collection of genetic markers evenly spaced across the genome. It does not require knowledge of the function of any genes, or the biology of the trait in question. Directed genomic screening means investigating certain areas/genes considered being of interest for the phenotype. The areas/genes of interest can be based on earlier studies, "educated guesses", or knowledge of the pathogenesis and function of earlier-identified genes.

The overall aim of this study was to identify genetic susceptibility loci for atopic dermatitis. We recruited families with at least two siblings affected with AD. DNA was obtained from 1097 affected siblings that together formed 650 affected sib pairs and 49 affected half-sib pairs. These were all examined and phenotyped. Of the affected siblings, 74% had raised total...
and/or allergen-specific serum IgE levels and 72% had asthma (I).

In the first part we studied linkage and association to six chromosomal regions (2q35, 3q21, 5q31, 6p21, 11q13, and 14q11), previously implicated as candidate regions in atopic diseases, and one new candidate gene, the gene for Wiskott-Aldrich syndrome located on Xp11 (II, III). These candidate genes were investigated in 572 affected sib pairs and 30 affected half-sib pairs (1514 individuals).

We also performed a random genomic screening with 367 microsatellite markers, using a non-parametric affected relative pair method (IV). One hundred and nine pedigrees were included, forming 193 affected full-sib pairs and 9 affected half-sib pairs (470 individuals).

We studied the following four phenotypes in the affected siblings. 1) AD as diagnosed according to the UK Working Party Diagnostic Criteria. 2) AD in combination with elevated allergen-specific serum IgE levels (sp-IgE+). 3) AD with a more severe phenotype (extreme AD). 4) The severity score of atopic dermatitis.

In the candidate genes, the region on 14q11 gave evidence for linkage to the phenotype extreme AD (p<0.005), in the WAS region. We could not replicate the previous findings of a major susceptibility gene to AD on 3q21 that has been reported of a German group.

In the random genomic screening, for the phenotype sp-IgE+, suggestive linkage (p<7x10^-4) was found to chromosome region 18q21. For the phenotype, severity score of atopic dermatitis, suggestive linkage was found to chromosome regions 3q14, 13q14, 15q14-15 and 17q21. For the phenotype AD, almost suggestive linkage to chromosome region 3p24-22 was found.

In conclusion, we have identified chromosome regions linked to susceptibility genes for AD. This provides a platform from which the search for AD genes can proceed.

List of original papers


