secretory granules of mast cells.

List of original publications

1. Kaminska R, Harvima IT, Naukkarinen A, Nilsson G, Horsmanheimo M. Alterations in mast cell proteinases and protease inhibitors in the progress of cutaneous herpes zoster infection. J Pathol 1996; 180: 434–440.
2. Kaminska R, Naukkarinen A, Glinski W, Horsmanheimo M, Harvima IT. Mast cells in developing subepidermal bullous diseases: emphasis on tryptase, chy mase and protease inhibitors. Acta Derm Venereol 1999; 79: 351–355.
3. Kaminska R, Helisalmi P, Harvima RJ, Naukkarinen A, Horsmanheimo M, Harvima IT. Focal dermal-epidermal separation and fibronectin cleavage in basement membrane by human mast cell tryptase. J Invest Dermatol 1999; 113: 567–573.
4. Kaminska R, Naukkarinen A, Horsmanheimo M, Harvima IT. Suction blister formation in skin after acute and repeated mast cell degranulation. Acta Derm Venereol 1999; 79: 191–194.

In addition, this thesis includes the results concerning tryptase and chymase activity in skin blisters induced by freezing with liquid nitrogen published in Tabel I of the following article:
Kivinen PK, Kaminska R, Naukkarinen A, Harvima RJ, Horsmanheimo M, Harvima IT. Release of soluble tryptase but only minor amounts of chymase activity from cutaneous mast cells. Exp Dermatol 2001; 10: 246–255.

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.


Maria Bradly exhibits her thesis before defending it.

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 AD ($p<0.009$). In the 11q13 region, there was an association to an intragenic marker in the high-affinity IgE receptor for the phenotype sp-IgE+ ($p<0.009$). For the severity score of AD, evidence in favon or of linkage was found to the 5q31-33 region with the highest linkage close to the marker D5S458 ($p<0.005$). We also found 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.

Maria Bradley defended her thesis on December 13, 2001 at the Department of Dermato-Venereology, Karolinska Institutet, Stockholm. Faculty Opponent was Professor Mattias Wjst from GSF National Research Center of Environment and Healt, Germany. Assistant Professor Carl-Fredrik Wahlgren acted as supervisor.

List of original papers

I. Bradley M, Kockum I, Söderhäll C, Van Hage-Hamsten M, Luthman H, Nordenskjöld M, Wahlgren. C-F. Characterization by phenotype of families with atopic dermatitis. Acta Derm Venereol 2000; 80: 106–110.

II. Söderhäll C, Bradley M, Wahlgren C-F, Luthman H, Kockum I, Nordenskjöld M. Linkage and association to candidate regions in Swedish atopic dermatitis families. Hum Genet 2001; 109: 129–135.

III. Bradley M, Söderhäll C, Wahlgren C-F, Luthman H, Nordenskjöld M, Kockum I. The Wiskott-Aldrich syndrome gene as a candidate gene for atopic dermatitis. Acta Derm Venereol 2001; 81: 340–342.

IV. Bradley M, Söderhäll C, Wahlgren C-F, Luthman H, Nordenskjöld M, Kockum I. Atopic dermatitis susceptibility loci on chromosomes 3, 13, 15 and 18 in a Swedish population. Hum Mol Med, in press 2002.