Genetic Studies on Psoriasis with Emphasis on the HLA Region

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Carlotta Enerbäck defended her thesis at Sahlgrenska University Hospital, Göteborg. At Faculty Opponent was Holger Luthman and Examinator was Professor Olle Larkö, Department of Dermatology, Sahlgrenska University Hospital, Göteborg, Sweden.

In collaboration with the Swedish Psoriasis Association, a large patient sample has been collected with blood samples for DNA analysis. The main purpose of the group has been to demonstrate the genetic contribution to the disease and to localise susceptibility genes.

Psoriasis is a heterogeneous disease in which several reports suggest the presence of a susceptibility gene in or in the proximity of the HLA complex in chromosome 6p. There is an association between HLA-Cw6 and young onset of the disease. The aim of this study was to evaluate the importance of HLA and in particular the Cw6 allele in the development of psoriasis.

We could confirm the presence of a gene in the HLA region by means of parametric and non-parametric linkage analysis in 104 families. Using the Transmission Disequilibrium Test, (TDT), which is a statistical association test, we found further support for this.

We used a PCR-based typing method for Cw6 and showed a strong association to young onset of the disease. We studied the age at onset of siblings discordant for the presence of Cw6 using the Wilcoxon signed rank test. This test was significant with a mean difference in age at onset of 8 years. The Cw6 allele was sequenced in individuals homozygous for Cw6 without finding any alterations from the consensus reference sequence. In all, 11 individuals homozygous for Cw6 were identified by a sequencing method. They had an earlier age at onset than heterozygotes, which we interpret as a tendency to a gene dose effect. We found support for the direct influence of Cw6 on age at onset, rather than a polygenic effect where every genetic component adds to the genetic load.

The S gene (corneodesmosin), located 160 kb telomeric of HLA-C, is a strong candidate for psoriasis due to its reportedly exclusive expression in differentiating keratinocytes. We found a high variability in the coding parts of the gene using sequencing analysis. We performed association tests such as TDT and case control analysis, and compared several polymorphisms among patients and controls using a stratification approach, in order to decrease the influence of heterogeneity and population differences. Based on TDT results of polymorphisms in the S gene, multiallelic markers in the HLA region and from the Cw6 allele *per se,* we conclude that Cw6 is likely to be the primary association in this region. However, further studies are required to evaluate if Cw6 itself or a gene in linkage disequilibrium with Cw6 is the factor in the HLA region determining age at onset.

We have also performed cytogenetic analysis of 477 unrelated psoriatics. We found 2 patients with a translocational breakpoint in 11q12-13, in a region where the major atopy locus as well as a locus for diabetes mellitus is located. The breakpoints were further characterised by fluorescent *in situ* hybridisation.

Key words: psoriasis, age at onset, HLA, HLA-Cw6, linkage analysis, transmission disequilibrium test, corneodesmosin, cytogenetics.

List of original publications

1. Enerbäck C, Martinsson T, Inerot A, Wahlström J, Enlund F, Yhr M, Swanbeck G. Evidence that HLA-Cw6 determines early onset of psoriasis obtained using sequence-specific-primers (PCR-SSP). Acta Derm Venereol 1997; 77: 273-276.
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6. Enerbäck C, Holmqvist D, Inerot A, Enlund F, Samuelsson L, Torinsson Å, Wahlström J, Swanbeck G, Martinsson T. Cytogenetic analysis of 477 psoriatics revealed an increased frequency of aberrations involving chromosome region 11q. Eur J Hum Genet 1999; 7: 339-344.

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Pityrosporum ovale (Malassezia furfur) and Atopic Dermatitis

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Dr Päivi Lintu (*centre*) defended her thesis at the Department of Dermatology, University of Turku. Faculty opponent was Associate Professor Kristiina Turjanmaa from Tampere (*left*) and Chairman was Professor Christer Jansén from the Department of Dermatology, University of Turku (*right*). Associate Professor Kirsti Kalimo (Department of Dermatology, University of Turku) and Associate Professor Johannes Savolainen (Department of Pulmonary Diseases and Clinical Allergology, University of Turku) supervised the Thesis.

ABSTRACT

Allergy to a saprophytic yeast of the human skin, *Pityrosporum ovale* (*P. ovale*), an oval form of Malassezia furfur, has been suspected to play a role in atopic dermatitis (AD), especially in patients with head, neck and shoulder dermatitis. The aim of this study was to investigate the importance of *P. ovale* as a source of allergens in adult patients with AD.