The heritability and atopic dermatitis

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ABSTRACT

The heritability of atopic disease – especially atopic dermatitis (AD), asthma and rhinitis are common diseases with increasing prevalence in the industrialized part of the world. The pathogenesis is multifactorial and poly- or oligogenic with a considerable and well documented heritability. Identification of disease susceptibility genes may increase our knowledge of the pathogenesis and thereby facilitate better diagnostic tools, treatment and prevention.

The aim of this dissertation was identification of genes for atopic dermatitis and other atopic phenotypes.

We performed association analyses of the IL2, IL15 and HRH1 genes in two previously collected samples comprising a total of 235 Danish atopic families, with significant results for IL2 and HRH1. Two single nucleotide polymorphisms (SNPs) in IL2 showed association with several allergic phenotypes, most significantly with type I allergy (single SNP P-value 0.0005 for positive skin prick test, haplotype P-value 0.019 for positive specific IgE). The SNP showing the most consistent results is located in the promoter and has previously been shown to influence the level of IL2 expression. We suggest that the observed overtransmission of the T allele of this SNP may convey increased susceptibility to allergic disease by skewing the Th1/Th2 balance towards Th2.

In HRH1, three SNPs showed significant association with eight phenotypes, most significant a two-marker haplotype with IgE-associated AD (p=0.0009). In silico analyses revealed an effect of the two promoter SNPs on potential binding sites for transcription factors suggesting a functional impact of the variants on gene expression.

We collected and genotyped a novel AD family sample including 130 Danish nuclear sib-pair families with at least 2 children with AD, a total of 555 persons. All persons were clinically examined and questionnaire tested by the same doctor. Atopic disease was diagnosed and an AD severity index was scored for each child. Blood was drawn for DNA extraction and serum measurement of specific IgE to 11 common allergens.

A chromosome scan was performed using 91 highly informative microsatellite markers on chromosomes 3,4 and 18 chosen due to our previous AD-linkage results on 3p, 4p and 18q. The main results of the scan of chromosomes 3, 4 and 18 were:

– linkage of AD to 3p24.3 (MOD: 4.6 with a model showing a tendency of paternal imprinting)
– linkage of IgE-associated AD to 3q13-21 (LOD: 3.3)
– localization on 4q22.1 of a new gene influencing AD severity (p: 0.0001)
– suggestive linkage at 3q13, 18q12 and 4q34-35.

In conclusion, we found significant association of atopic phenotypes with SNPs in the IL2 and HRH1 genes suggesting the two genes as novel susceptibility genes for atopic disease. We collected an AD family sample and found linkage of AD and allergy to several chromosome regions, of which the AD severity region points to the localization of a novel AD gene.