Network: Diseases Due to Environmental Factors

Project: Genetic Determinants of Atopic Dermatitis and Allergic Disease

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Introduction

Atopic dermatitis is a chronic inflammatory skin disease that is characterized by intense itching. In the industrialized countries the prevalence of atopic dermatitis approximately 15% with a steady increase over the last decades. Along with asthma and allergic rhinitis, atopic dermatitis is an important manifestation of atopy that is characterized by the formation of allergy antibodies (IgE) to environmental allergens.

Atopic dermatitis is commonly the first clinical manifestation of allergic disease. Onset of disease is observed during the first year of life in 57% and during the first five years in 87% of patients. For the majority of affected children atopic dermatitis heralds a lifetime of allergic disease. The development of atopic disease often follows an age-dependent pattern that is known as the "atopic march". A susceptible child commonly passes a characteristic sequence of transient or persistent disease stages that begins with atopic dermatitis and food allergy in the young infant and continues with the development of respiratory airways disease later in childhood and adulthood.

A strong genetic component in atopy and has been recognized. The strongest epidemiological evidence for the importance of genetic factors in atopic disease stems from twin studies. The concordance rate for atopic dermatitis among monozygotic twins of about 80% far exceeds the concordance rate of 20% observed among dizygotic twins. These data clearly indicate that the genetic contribution to the expression of atopic dermatitis is substantial. In addition, studies on the vertical transmission of atopic dermatitis and atopic disease show that children are more likely to inherit these disorders if the mother is affected (parent-of-origin effect). Atopic dermatitis and atopic disorders are complex genetic traits in which the interaction of several major and minor disease susceptibility genes with environmental factors determines the manifestation and severity of atopic dermatitis.

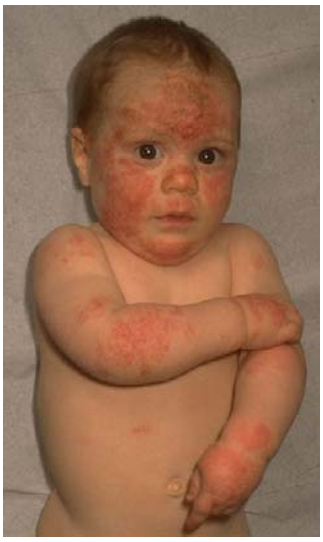

Fig 1: *The first step in the "Atopic March": Infantile atopic dermatitis.*

Results/Project Status

Clinical phenotyping

Infantile atopic dermatitis is an important risk factor for the development of asthma and hayfever. Most of the index children were below school age at the time of initial enrollment in the study and may not yet have manifested allergic airways disease. The goal of the clinical phenotyping group is therefore to perform a prospective reevaluation of the families for atopic dermatitis and allergic airways disease by questionnaires, physical examination, and lung function testing. To obtain additional sub-phenotypes, a subset of families is being investigated for genome-wide gene expression levels from peripheral blood leukocytes.

Dissection of a locus for atopic dermatitis on chromosome 3q21

We have previously mapped a major susceptibility locus for atopic dermatitis (NPL = 4.31, P = 8,42 x 10-6) to chromosome 3q21. This locus also provided significant evidence for linkage of allergic sensitization under the assumption of paternal imprinting.

Strong functional candidate genes within the 90% support interval of the AD locus were investigated for association with the disease phenotypes. CD80 and CD86 are type 1 membrane proteins of the immunoglobin superfamily that mediate important costimulatory signals for T cell activation and have been implicated in the activation of the Th2 subset of CD4+ T helper lymphocytes that play a pivotal role in mediating allergic inflammation. Genetic polymorphisms were evaluated for association with atopic dermatitis and atopy and no association with AD or atopy was detected.

Subregions on chromosome 3q21 were prioritized according to gene content for SNP identification and genotyping. In view of the overlapping linkage findings for the chronic inflammatory skin diseases atopic dermatitis and psoriasis, a 1,2 Mb subregion surrounding the SLC12A8 gene was targeted that had been shown to be linked and associated with psoriasis in a Swedish cohort. Microsatellite markers and SNPs in the region were examined for association with atopic dermatitis and atopy. No significant association was detected. We conclude that on chromosome 3q21 distinct genetic determinants for atopic dermatitis and psoriasis are operative and that the overlap of linkage findings may reflect close linkage of functionally related genes.

We have used the positional cloning approach to identify the susceptibility gene for atopic dermatitis on chromosome 3q21. To obtain higher resolution in the candidate region linkage disequilibrium mapping has been performed. Genetic markers have been identified by sequence analysis and have been selected for genotyping. The family cohorts recruited in the NGFN during the first funding period are being used to replicate positive association findings.

Evaluation of GPRA in atopic dermatitis

The common genetic background of the allergic diseases is reflected by the atopic march in which a susceptible child passes a characteristic sequence of transient or persistent disease stages that begins with atopic dermatitis in the young infant and continues with the development of asthma and allergic rhinitis later in life. The close familial and intra-individual association of these disease entities strongly suggests shared genetic determinants. Recently, the gene encoding G protein-coupled receptor for asthma susceptibility (GPRA) was shown to be involved in the

pathogenesis of atopy and asthma. The expression pattern of the disease associated B isoform, including tissues commonly associated with allergic reactions, such as skin keratinocytes, bronchial smooth muscle cells, bronchial epithelium, and intestinal epithelium, render the GPRA gene a prime candidate for the joint genetic origin of allergic disease. We have therefore evaluated the GPRA gene as a genetic risk factor for atopic dermatitis.
Using two large European family cohorts including 826 children with atopic dermatitis, we conducted a family-based association test to avoid potential sources of error due to population admixture or stratification. No association with atopic dermatitis was detected. We conclude that the GPRA risk-haplotypes for asthma do not play a major role in the development of atopic dermatitis and that the GPRA gene does not contribute to the shared genetic predisposition of atopic dermatitis and allergic airways disease in our study population.

Animal models

Animal models offer the unique possibility to study molecular mechanisms of allergic diseases such as atopic dermatitis in whole organisms. We have contributed to the generation of a SNP map based on transcribed sequences for the rat which is one of the most important animal models for complex human disease and pharmacology.

Outlook

The identification of genes underlying atopic dermatitis and and atopy has the capacity to characterize primary disease mechanisms and to define novel molecular pathways that provide targets for preclinical diagnosis, disease prevention, and therapeutic intervention.

*Lit.: **1.** Lee YA et al. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. Nat Genet. 2000; 26(4): 470-473 **2.** Söderhäll C et al. Lack of association of the GPRA (G protein-coupled receptor for asthma susceptibility) gene with atopic dermatitis. J All Clin Immunol 2005;116(1):220-1. **3.** Rat Sequencing Consortium. Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature. 2004; 428(6982): 493-521. **4.** Zimdahl H et al. A SNP map of the rat genome generated from cDNA sequences. Science. 2004; 303(5659): 807.*