Network: Diseases Due to Environmental Factors

Project: Atopic Dermatitis: Systematic Exploration of the Linkage Regions on 5q31-q33, 6p11-21 and 10q23

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Introduction

The disease

Atopic dermatitis (AD) is a hereditary pruritic chronic relapsing inflammatory skin disease frequently associated with atopic manifestations such as allergic asthma and allergic rhinoconjunctivitis (reviewed in: Novak et al., 2003). Typically the atopic state is characterized by immunglobuling E (IgE) response against common allergens and by elevations of total serum IgE concentrations. The incidence of AD during childhood has increased 5-10 fold over the past four decades to up to 15 % in the industrialized countries. AD results from complex interactions between several genetic and environmental risk factors. Twin studies indicate a strong genetic risk factor resulting in a concordance rate of 0.86 for monozygotic twins in comparison with 0.21 for dizygotic twins. During the past few years, in systematic genome scans several chromosomal regions linked to atopic diseases have been repeatedly found in Caucasian populations (reviewed in Cookson et al., 2002 and Cookson et al., 2004; Lee et al., 2002; Bradley et al., 2002).

Regions linked to various chronic inflammatory diseases

Assuming that susceptibility loci implicated in chronic inflammation processes play a role in different diseases (cross-disease approach) we will systematically explore the chromosomal regions 5q31, 6p21 and 10q23, which are, among others, linked to AD, Inflammatory Bowel Disease (IBD), psoriasis and sarcoidosis. 5q31 comprises several genes encoding proteins involved in inflammatory processes, such as IL4, IL9, IL13, GM-CSF and CD14. Recently we could exclude SPINK5, a gene on 5q31, which was found to be associated with the Netherton's syndrome, a rare recessive disease characterized by congenital ichthyosiform erythroderma and atopic diathesis (Fölster-Holst et al., 2005).

The major histocompatibility complex (MHC) region on chromosome 6p21 is suggested to harbour susceptibility genes for psoriasis (PSOR1) and AD (Söderhall et al., 2001). Furthermore, the region comprises several genes involved in immune-mediated complex diseases such as tumor necrosis factor alpha (TNFα) and butyrophilin-like 2 (BTNL2) gene, which is mutated in patients with sarcoidosis, a mulisystematic immune disorder (Valentonyte et al., 2005).

Recently the DLG5 gene on 10q23 was identified as a susceptibility gene for IBD (Stoll et al., 2004). The gene encodes a membrane-associated guanylate kinase, which plays a role in maintaining the structure of epithelial cells and transmitting extracellular signals to the membrane and cytoskeleton.

These three linkage regions will be genotyped on the basis of already established haplotype structures followed by a high-density SNP mapping of the identified lead regions and mutation detection.

Methods and Results

We recruited one of the largest collection for AD patients worldwide, comprising 1,228 unrelated single cases and 491 trios. The diagnosis of AD was established according to the criteria of Hanifin and Rajka (Hanifin and Rajka 1980). The severity of AD in patients was determined by SCORAD (SCORAD index 1993). Power calculations using the algorithms described by Sham et al. (2000) and implemented in the software by Purcell et al. (2003) revealed that both study samples, case control and nuclear families/trios, are sufficiently powered to detect an association for the 5q31 region (IBD5) as well as for DLG5.

For genotyping we have applied the TaqMan allelic discrimination assay in the 384-plate scale as described previously (Hampe et al., 2002). Each marker first has been subjected to single-locus tests for linkage and TDT analysis followed by haplotype analysis using GENEHUNTER (Vs.2.1) and HAPLOVIEW (Vs.3.2) to test for association with AD. In addition, we have analysed the sample for parent-of-origin effects as implemented in GENEHUNTER. Single point case-control analyses has been performed using an in-house tool that creates contingency table tests for genotype and allele frequencies and also provides empirical significances for p-values as well as confidence intervals for odds ratios through randomization and bootstrapping. We have assessed the extended haplotype structure underlying these lead regions and have tested for the association with AD, IgE levels and age-of-onset and other clinical features.

For DLG5 neither in TDT nor in case-control study an association to AD could be found. In contrast, according to known risk haplotype structures (Giallourakis et al., 2003) genotyping of IBD5 and bordering regions on 5q31 revealed a significant association (p=0.0019) to AD, exclusively for the paternal transmission. In contrast, CD14 on 5q31, which was repeatedly discussed as a candidate gene for AD and asthma (Feijen et al., 2000), showed no association.

Outlook

Upcoming, the results of the genotyping of 5q31 will be replicated using additional 480 German AD trios from the German Atopic Dermatitis Consortium which includes the Max-Delbrück-Centrum, Berlin, the Department of Dermatology and Allergy of the Technical University Munich., the Department of Dermatology, University Clinics Schleswig-Holstein, Campus Kiel, and the Institute of Clinical Molecular Biology, Christian-Albrechts University, Kiel. Subsequently the causative genetic variant and its functional impact will be determined. Furthermore, the systematic exploration of the pre-HLA region on 6p21 is in progress.

Lit.: ***Key publications from Kiel - 1.*** *Fölster-Holst R, Stoll M, Koch WA, Hampe J, Christophers E, Schreiber S. (2005) Lack of association of SPINK5 polymorphisms with nonsyndromic atopic dermatitis in the population of Northern Germany. Br J Dermatol.152(6):1365-7.* ***2.*** *Stoll M, Corneliussen B, Costello CM, Waetzig GH, Mellgard B, Rosenstiel P, Albrecht M, Croucher PJP, Seegert D, Nikolaus S, Hampe J, Lengauer T, Pierrou S, Foelsch UR, Mathew CG, Lagerstrom-Fermer M, Schreiber S. (2004) Genetic variation in DLG5 confers susceptibility to inflammatory bowel disease. Nat Genet.; 36(5):476-80.* ***3.*** *Valentonyte R, Hampe J, Huse K, Rosenstiel P, Albrecht M, Stenzel A, Nagy M,Gaede KI, Franke A, Haesler R, Koch A, Lengauer T, Seegert D, Reiling N, Ehlers, S, Schwinger E, Platzer M, Krawczak M, Muller-Quernheim J, Schurmann M, Schreiber S. (2005) Sarcoidosis is associated with a truncating splice site mutation in BTNL2. Nat Genet. 37(4):357-64.* ***4.*** *Hampe J, Grebe J, Nikolaus S, Solberg C, Croucher PJP, Mascheretti S, Jahnsen J, Moum B, Klump B, Foelsch UR, Krawczak M, Foelsch UR, Vatn M, Schreiber S (2002). Association of NOD2 (CARD 15) genotype with clinical course of Crohn's disease: a cohort study. Lancet 359, 1661-1665.*

NGFN Nationales Genomforschungsnetz

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

Cited literature – 1. *Cookson W. (2004) The immunogenetics of asthma and eczema: a new focus on the epithelium.Nat Rev Immunol. 4(12):978-88.* ***2.*** *Cookson WO, Moffatt MF. (2002) The genetics of atopic dermatitis.Curr Opin Allergy Clin Immunol.2(5):383-7.* ***3.*** *Lee YA, Wahn U, Kehrt R, Tarani L, Businco L, Gustafsson D, Andersson F, Oranje AP, Wolkertstorfer A, v Berg A, Hoffmann U, Kuster W, Wienker T, Ruschendorf F, Reis A. (2000) A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. Nat Genet. 26(4):470-3.* ***4.*** *Bradley M, Soderhall C, Luthman H, Wahlgren CF, Kockum I, Nordenskjold M. (2002) Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. Hum Mol Genet. 11(13):1539-48.* ***5.*** *Söderhall C, Bradley M, Kockum I, Wahlgren CF, Luthman H, Nordenskjold M. (2001) Linkage and association to candidate regions in Swedish atopic dermatitis families. Hum Genet. 109(2):129-35.* ***6.*** *Hanifin JM, Rajka G (1980). Diagnostic features of atopic dermatitis. Acta Derm Venereol 92, 44-47.* ***7.*** *Severity scoring of atopic dermatitis: the SCORAD index (1993). Consensus report of the European Task Force on Atopic Dermatitis. Dermatology 186, 23-31.* ***8.*** *Sham PC, Cherny SS, Purcell S, Hewitt JK. (2000) Power of linkage versus association analysis of quantitative traits, by use of variance-components models, for sibship data. Am J Hum Genet. 66(5):1616-30.* ***9.*** *Purcell S, Cherny SS, Sham PC. (2003) Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. Bioinformatics. 19(1):149-50.* ***10.*** *Feijen M, Gerritsen J, Postma DS. (2000) Genetics of allergic disease. Br Med Bull. 56(4):894-907.*