Network: Diseases Due to Environmental Factors

Project: Systematic Association Mapping on Chromosomes 16p/q, 3p and the Perizentromeric Region on Chromosome 12 (IBD 1-3)

Jochen Hampe, Peter Croucher, Silvia Mascheretti, Andreas Ruether, Susanna Nikolaus, Stefan Schreiber, – Institut für Klinische Molekularbiologie, Christian-Albrechts-Universtität Kiel – j.hampe@mucosa.de ; s.schreiber@mucosa.de

Introduction

The disease

Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD) of largely unknown etiology. IBD is characterized by a chronic relapsing activity with problem-free phases ("remission") intervening with phases of inflammatory activity ("flair"). The clinical features include abdominal pain, (bloody) diarrhea and complications such as groth retardation in children, anemia, toxic megacolon and stenosis and fistulae (in Crohn disease). While some patients develop a chronically active disease in which inflammatory activity of different degrees is always present, others come to a complete clinical remission between active episodes. The immunological causes responsible for the different types of disease behavior are unclear and the triggers for the development of relapses are unknown.

IBD is a disease with rising incidence. The disease was unknown before the 1930ies. The prevalence is about 0.5% and the average manifestation age is within the 2nd to 4th decade of life. The genetic component of IBD has been clearly demonstrated by the consistent familial clustering and the concordance of the phenotype among monozygotic twins (concordance rates of ~50%) as compared to dizygotic twins (concordance rates of 4%). Epidemiological evidence suggests that genetic causes predispose to disease and also may determine the type of disease (clinical course, anatomic localization of inflammation).

State of genetic research in IBD

Genome wide linkage studies including our own (Hampe et al. 1999) have established replicated susceptibility regions on chromosomes 1, 3, 6, 7, 12 and 16. It is clear, that IBD is a polygenic -complex- disorder.

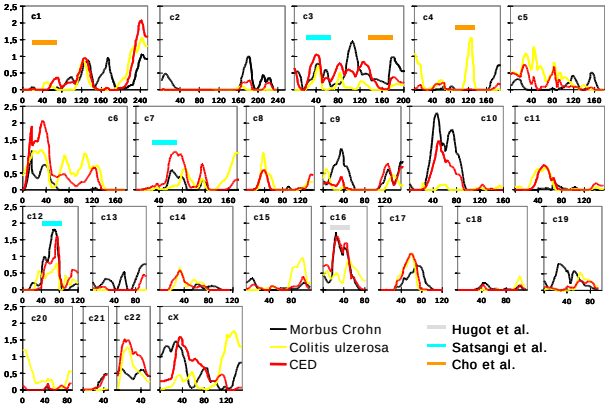


Fig 1: *The figure above depicts the results of the genome wide scan of the applicants. The results of three earlier genome wide scans are marked with colored bars in the figure.*

The figure above depicts the results of the genome wide scan of the applicants. The results of three earlier genome wide scans are marked with colored bars in the figure.

The genetic field in IBD has received a significant boost through the identification of the first gene for CD in 2001 (Hugot et al., 2001, Ogura et al., 2001, Hampe et al., 2001). There is an active international IBD genetics consortium, that is working on the replication of linkage and candidate gene findings. Therefore, there is an established set of replicated linkage regions, that provide targets for gene finding experiments through LD mapping within the NGFN2 framework (extensive genome scan and replication literature not cited due to space constraints). On the other hand, there is internationally tough competition in the IBD genetics field, as also shown by the involvement of major research institutions like the Whitehead (MIT), CEPH, Oxford university and the universities of Chicago and Baltimore (Johns Hopkins).

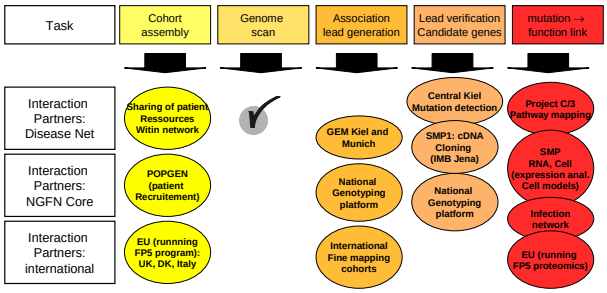
Results/Project Status

Phenotype validation

The applicants have an established clinical expertise in the IBD field. The Kiel center has coordinated multiple international clinical trials in the IBD field as documented by multiple publications (Schreiber et al, 1996; Probert et al., 2003; Tilg et al., 2002; and others, see literature list below). Within the recruitment projects, strict phenotyping criteria were established. A major factor in driving phenotype standardization was the competence network for IBD (BMBF funded, project was coordinated from Kiel), for which unified clinical criteria were established and employed during recruitement. Similar procedures are in place in the recruitement of the other European cohorts as part of a 5th framework programme IBD grant. Within the NGFN, there is an SOP for the IBD recruitment effort. There is a number of dedicated publications from the Kiel group, that have looked at the clinical and epidemiological data of our cohorts and have addressed specific phenotyping issues (Hampe et al., 2003, Hampe et al., 2001).

Project interactions

The IBD positional cloning projects use multiple resources from the NGFN network. A graphical overview is given below. Many network interactions are also handled through subprojects in our own network – these projects handle the bundled bioinformatic and functional agendas of the network. These agendas are of critical importance as the establishment of a clear functional link between a causative SNP and the disease phenotype is the ultimate goal of this positional cloning network.



Overview of the interaction of the IBD projects at various stages of the gene discovery process.

Positional cloning results

The Kiel group was involved in the CARD15 gene identification. The centre also first published a genotype-phenotype analysis of CARD15 in CD. Further, the applicants have identified the first IBD disease gene on chromosome 10 – DLG5 (Stoll et al., 2004). We further first described evidence of CARD15-independent disease gene on chromosome 16. These findings have since been replicated by two other groups (van Heel et al., 2003, Annese et al., 2003).

Currently a number of additional linkage regions and association leads are under investigation.

*Lit.: **Key publications from Kiel - 1.** 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. **2.** Mascheretti S, Hampe J, Kuhbacher T, Herfarth H, Krawczak M, Folsch UR, Schreiber S. Pharmacogenetic investigation of the TNF/TNF-receptor system in patients with chronic active Crohn's disease treated with infliximab. Pharmacogenomics J. 2002;2(2):127-36. **3.** Hampe J, Frenzel H, Mirza MM, Croucher PJP, Cuthbert A, Mascheretti S, Huse K, Platzer M, Bridger S, Meyer B, Nürnberg P, Stokkers P, Krawczak M, Mathew CG, Curran M, Schreiber S (2002). Evidence for a NOD2 independent susceptibility locus for Inflammatory Bowel Disease on Chromosome 16p. Proc Nat Acad Sci USA 99: 321-326. **4.** Hampe J, Cuthbert A, Croucher PJP, Mirza MM, Mascheretti S, Fisher S, Frenzel H, King K, Hasselmeyer A, MacPherson AJS, Bridger S, Deventer SJH, Forbes A, Nikolaus S, Lennard-Jones JE, Foelsch UR, Krawczak M, Lewis C, Schreiber S, Mathew CG (2001). An insertion mutation in the NOD2 gene predisposes to Crohn's Disease in the German and British populations. Lancet 357: 1925-1928 **5.** Rosenstiel P, Fantini M, Bräutigam K, Kühbacher T, Waetzig GH, Seegert D and Schreiber S (2003). TNF-a and IFN-g regulate the expression of the NOD2 (CARD15) gene in human intestinal epithelial cells. Gastroenterology 124(4): 1001-9 **6.** 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. Genetic variation in DLG5 confers susceptibility to inflammatory bowel disease. Nat Genet. 2004; 36(5):476-80.*

***Cited literature – 1.** Annese V, Latiano A, Palmieri O, Li HH, Forabosco P, Ferraris A, Andriulli A, Vecchi M, Ardizzone S, Cottone M, Dallapiccola B, Rappaport E, Fortina P, Devoto M (2003) Linkage of ulcerative colitis to the pericentromeric region of chromosome 16 in Italian inflammatory bowel disease families is independent of the presence of common CARD15 mutations. J Med Genet 40:837-841. **2.** Duerr RH, Barmada MM, Zhang L, Davis S, Preston RA, Chensny LJ, Brown JL, Ehrlich GD, Weeks DE, Aston CE (1998) Linkage and Association between Inflammatory Bowel Disease and a Locus on Chromosome 12. Am J Hum Genet 63:95-100. **3.** Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 411:599-603. **4.** Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH (2001) A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 411:603-606. **5.** Ogura Y, Inohara N, Benito A, Chen FF, Yamaoka S, Nunez G (2001) Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF{kappa}B. J Biol Chem 276:4812-4818 **6.** Satsangi J, Parkes M, Louis E, Hashimoto L, Kato N, Welsh K, Terwilliger JD, Lathrop GM, Bell JI, Jewell DP (1996) Two stage genome-wide search in inflammatory bowel disease provides evidence for susceptibility loci on chromosomes 3, 7 and 12. Nat Genet 14:199-202 **7.** Schreiber S, Howaldt S, Schnoor M, Nikolaus S, Bauditz J, Gasche C, Lochs H, Raedler A (1996) Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. N Engl J Med 334:619-623 **8.** Tilg H, van Montfrans C, van Den Ende A, Kaser A, van Deventer SJ, Schreiber S, Gregor M, Ludwiczek O, Rutgeerts P, Gasche C, Koningsberger JC, Abreu L, Kuhn I, Cohard M, LeBeaut A, Grint P, Weiss G (2002). Treatment of Crohn's disease with recombinant human interleukin 10 induces the proinflammatory cytokine interferon gamma. Gut 50: 191-195. **9.** van Heel DA, Dechairo BM, Dawson G, McGovern DP, Negoro K, Carey AH, Cardon LR, Mackay I, Jewell DP, Lench NJ (2003) The IBD6 Crohn's disease locus demonstrates complex interactions with CARD15 and IBD5 disease-associated variants. Hum Mol Genet 12:2569-2575*