Disease-oriented Genome Networks

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)

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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 fistulas (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.

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.

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, Tlig 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 recruitment. Similar procedures are in place in the recruitment 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.

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.
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.
