Wilhelm Johannsen Centre for Functional Genome Research
University of Copenhagen

Identification of a chromosomal breakpoint at 12q14.1-12q14.2 in a patient with Crohn's Disease

D. Brudzewsky[1], N. Tommerup[1], C. Lundsteen[2], H.H. Ropers[3], S. Schreiber[4] , Z. Tümer[1]*

[1] Wilhelm Johannsen Centre for Functional Genome Research, IMBG, The Panum Institute, University of Copenhagen (Denmark); [2] Cytogenetic Laboratory, Department of Medical Genetics, Juliane Marie Center, The National University Hospital, Copenhagen (Denmark); [3] Max-Planck Institute of Molecular Genetics, Berlin (Germany); [4] 1st Medical Department, Christian-Albrechts-University, Kiel (Germany) * dan@medgen.ku.dk

Summary
We hereby present the preliminary results of cytogenetic and Fluorescence In-Situ Hybridisation (FISH) analysis of a patient with Crohn's disease and a balanced chromosomal translocation where the karyotype is t(10;12). The chromosome 12 breakpoint is within the putative susceptibility area for inflammatory bowel disease (IBD2). We anticipate that further refinement of the chromosome 12 breakpoint may reveal candidate genes for IBD2.

Introduction
Crohn's disease (CD; MIM 266600) and ulcerative colitis (UC; MIM 191390) are two major clinical forms of the multifactorial disorder chronic inflammatory bowel disease (IBD).
A definitive classification of Crohn's disease and ulcerative colitis is in some cases impossible. In Crohn's disease the bowel inflammation is transmural, discontinuous and may involve any part of the gastrointestinal tract, whereas in ulcerative colitis the bowel inflammation is continuous but limited to the rectal and colonic mucosal layers. In both diseases patients may have extraintestinal inflammation of the skin, eyes, or joints.
Eight different susceptibility loci for CD and/or UC have been suggested in several independent studies and the first susceptibility gene for CD, *NOD2,* has been identified [1,2,3].

Karyotype of the patient
The karyotype of our patient was 46,XX,t(10;12)(q25;q14)pat, with the chromosome 12 breakpoint within the IBD2 susceptibility region (12p13.2-q24.1)(MIM 601458). Our patient's parents are phenotypically normal.

FISH results
The IBD2 region is suggested by multiple independent linkage studies to cover an approximately 35Mb region and show mainly susceptibility to UC. The DNA marker D12S83, which maps to 12q14.1, gives the highest LOD score (5.47) for IBD2 [4]. This result has been sustained by its replication in an independent study [5]. The *AVIL* gene has been tested as a possible candidate gene for IBD by our group. The gene maps to 12q14 in the IBD2 region and the putative gene product (Avillin) share homology to the Villin protein. The Villin mRNA is expressed in simple epithelia of some tissues of the gastrointestinal and urogenital tracts [9] whereas the mRNA of the AVIL gene is expressed in the intestine. Mutation screening of unrelated patients with linkage to chromosome 12 have excluded AVIL as the IBD2 gene [6].
By FISH, the chromosome 12 breakpoint has been mapped to an approximately 5 Mb region. The breakpoint is at the moment defined by the BACs RP11-318E11 and RP11-221N13 that hybridised proximal and distal to the chromosome 12 breakpoint, respectively (Figure 1 and 2). The proximal BAC includes the DNA marker D12S83 which indicate that the breakpoint could be located in the vicinity of, or within possible candidate genes for IBD2.

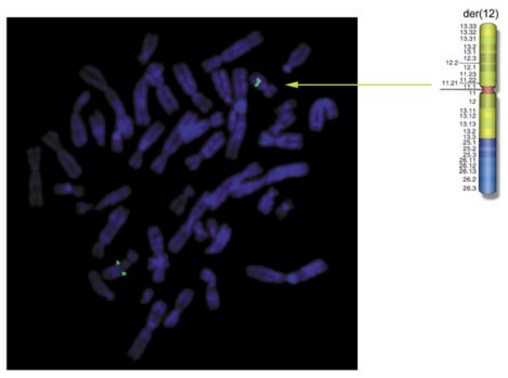

Figure 1

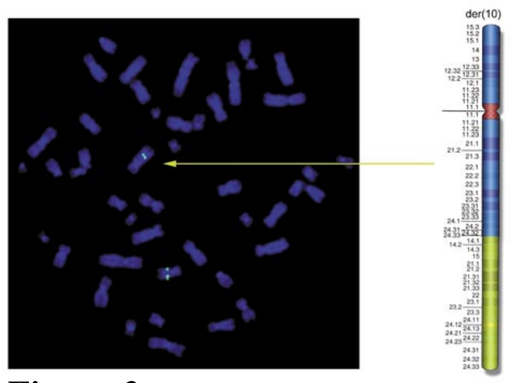

Figure 2

Discussion
Linkage analysis of IBD strongly supports that a candidate gene for mainly UC is located in the vicinity of the DNA marker D12S83. Here we present a CD patient with a chromosomal breakpoint distal to the DNA marker D12S83. That the phenotypically normal father has the same translocation as the CD patient may indicate that the translocation is a coincidental finding, or alternatively, that the phenotypical differences between our patient and her father could be due to sex differences, differences in carrier status of other susceptibility genes and/or differences in environmental factors involved in the physiopathology of IBD.
The gene found to be affected by the chromosomal breakpoint might play a minor role in the physiopathology of IBD. The known association of IBD2 with mainly UC could indicate that the involved gene(s)/type of mutation do not result in a severe inflammation, whereas in our case we can expect a complete knockout of the gene(s) which might explain why the patient suffers from CD instead of UC.

Future work will include narrowing of the breakpoint region by further FISH studies to identify genes that may be affected by the translocation. However the study has been complicated due to unfinished human genome sequencing and the contigs within this region have been changed several times during the study. The latest announcement of the finished human genome sequence will enable the mapping of this breakpoint in the very near future. Any candidate gene identified by the subsequent study will be tested by mutation screening of patients and molecular biological experiments. The present translocation represents a unique possibility to identify an IBD candidate gene with low penetration which can supply further pieces to the etiological puzzle of IBD. It also support the notion that constitutional chromosomal rearrangements may be associated with multifactorial, late onset disorders.

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