# A Genomewide Analysis Provides Evidence for Novel Linkages in Inflammatory Bowel Disease in a Large European Cohort

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## Summary

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing intestinal inflammation, typically starting in early adulthood. IBD is subdivided into two subtypes, on the basis of clinical and histologic features: Crohn disease and ulcerative colitis (UC). Previous genomewide searches identified regions harboring susceptibility loci on chromosomes 1, 3, 4, 7, 12, and 16. To expand our understanding of the genetic risk profile, we performed a 9-cM genomewide search for susceptibility loci in 268 families containing 353 affected sibling pairs. Previous linkages on chromosomes 12 and 16 were replicated, and the chromosome 4 linkage was extended in this sample. New suggestive evidence for autosomal linkages was observed on chromosomes 1, 6, 10, and 22, with LOD scores of 2.08, 2.07, 2.30, and 1.52, respectively. A maximum LOD score of 1.76 was observed on the X chromosome, for UC, which is consistent with the clinical association of IBD with Ullrich-Turner syndrome. The linkage finding on chromosome 6p is of interest, given the possible contribution of human leukocyte antigen and tumor necrosis–factor genes in IBD. This genomewide linkage scan, done with a large family cohort, has confirmed three previous IBD linkages and has provided evidence for five additional regions that may harbor IBD predisposition genes.

## Introduction

Inflammatory bowel disease (IBD; MIM 601458, 266600, 191390) is a disorder of unknown etiology, characterized by chronic relapsing inflammation of the gastrointestinal tract. IBD is categorized into two main subtypes, on the basis of clinical and histopathologic features: Crohn disease (CD; MIM 266600) and ulcerative colitis (UC; MIM 191390; Hamilton 1987; Podolsky 1991). Clinical features include abdominal pain, chronic diarrhea, rectal bleeding, weight loss, intestinal stenoses, fistulae, and toxic megacolon. IBD is also associated with extraintestinal manifestations, such as arthritis and uveitis (Nordgren et al. 1992). The disease incidence peaks in early adulthood and is rising worldwide, with a current prevalence of ~1/1,000 in Western countries (Probert et al. 1996; Shivananda et al. 1996).

Although the cause of IBD is unknown, a strong genetic susceptibility for IBD is shown by both consistent familial clustering of disease (Mayberry 1989; Orholm et al. 1991; Colombel et al. 1996; Satsangi et al. 1996a) and increased concordance in monozygotic twins (Tysk et al. 1988; Thompson et al. 1996). Significant prevalence differences exist among different ethnic groups living in the same geographic region, displayed by the two- to eightfold higher prevalence in Ashkenazi Jews versus non-Jews (Roth et al. 1989). Epidemiologic and clinical features, such as the association with Ullrich-Turner syndrome (Price 1979; Arulanantham et al. 1980; Hayward et al. 1996), cannot be explained on the basis of the available genetic data. Estimates of sibling risk ($\lambda_s$) show a range of 10–50, suggesting that genetic factors play a significant role in predisposition to IBD (Fielding 1986; Orholm et al. 1993; Peeters et al. 1996). A simple genetic model of IBD inheritance has not been supported by segregation analysis, suggesting a more complex pattern of inheritance (Kuster et al. 1989; Orholm et al. 1993),

**Table 1**

Overview of the Family Cohort

| SIBSHIP SIZE | CD | | | UC | | | MIXED CD/UC | | | TOTAL ASPs (ALL) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Complete | Incomplete Parents | Total CD ASP | Complete | Incomplete Parents | Total UC ASP | Complete | Incomplete Parents | Total Mixed ASPs | |
| 2 | 55 (55) | 59 (59) | 114 (114) | 36 (36) | 42 (42) | 78 (78) | 17 (17) | 21 (21) | 38 (38) | 230 (230) |
| 3 | 5 (15) | 9 (27) | 14 (42) | 4 (12) | 8 (24) | 12 (36) | 2 (6) | 7 (21) | 9 (27) | 35 (105) |
| 4 | 1 (6) | … | 1 (6) | … | … | … | 1 (6) | 1 (6) | 2 (12) | 3 ( 18) |
| Total | 61 (76) | 68 (86) | 129 (162) | 40 (48) | 50 (66) | 90 (114) | 20 (29) | 29 (48) | 49 (77) | 268 (353) |

NOTE.—Affected sibling pairs (ASP) are ordered according to sibship size and disease type within the family. "Mixed" denotes sibships with both UC and CD. Numbers in parentheses are the number of sibships and affected sib pairs. The availability of parents for the analysis of allele sharing identical by descent is indcated for each subgroup in the column marked "incomplete parents."

caused by multiple susceptibility genes and environmental factors (Koutroubakis et al. 1996).

Previous genomewide linkage analyses in 78 and 160 families of white northern European extraction (111 and 186 affected sibling pairs, respectively) defined candidate regions on chromosomes 3, 7, 12, and 16 (Hugot et al. 1996; Satsangi et al. 1996b). The importance of the candidate regions on chromosomes 12 and 16 has been confirmed by subsequent studies (Ohmen et al. 1996; Curran et al. 1998; Duerr et al. 1998; Mirza et al. 1998). A recent study using allele-sharing methods in 151 sib pairs, as well as in 146 distant relative pairs, suggested additional susceptibility loci on chromosomes 1p, 3q, and 4q (Cho et al. 1998).

To further develop an understanding of the genetic basis of IBD, we have assembled 353 affected sibling pairs from 268 white northern European families (United Kingdom, Germany, and the Netherlands). We describe here the results of a genomewide search for IBD susceptibility loci in this large collection of families.

## Families and Methods

### Family Ascertainment and Phenotypes

An international consortium identified and sampled kindreds with ≥2 affected siblings given diagnoses of IBD. Patients were recruited from IBD programs at King's College School of Medicine, Guy's Hospital, and St. Mark's Hospital (London); Charite University Hospital (Berlin); Academic Medical Center (Amsterdam); and other central European medical centers and through national patient organizations in Germany and the United Kingdom. Written informed consent was obtained from all study participants. Recruitment protocols were approved by institutional review committees at each participating center. The diagnosis of IBD and the classification into CD or UC were determined by standard diagnostic criteria, as described by Lennard-Jones (1989) and Podolsky (1991). Ascertainment criteria were determined prior to the initiation of patient

collection. For families originating from the United Kingdom and the Netherlands, medical records for all patients were reviewed by one or more of the principal investigators. For families of German extraction, possible patients were directly examined by one or more of the principal investigators. Alternatively, two written records, containing a detailed disease history and results of all diagnostic procedures, were obtained for each patient and reviewed by the principal investigators. A venous blood sample was obtained from the affected siblings and their parents, if possible. An overview of the family cohort is given in table 1.

### Genotyping

Genomic DNA was prepared from whole blood with the Puregene system (Gentra Systems). A total of 358 highly polymorphic microsatellite markers, providing genome coverage at an average density of 1/9.4 cM (range 4–23.7 cM), were genotyped with fluorescent methods, as described by Hall and Nanthakumar (1997). In brief, individual DNA samples were arrayed in 96-well microtiter plates and subjected to amplification by PCR, with individual marker amplicons. The amplified products were pooled, heat denatured, and subjected to electrophoresis on denaturing polyacrylamide gels. We collected data using ABI 377 automated DNA sequencers, and we performed data analyses using GENESCAN (version 2.1) and GENOTYPER (version 1.1.1). Allele analyses and individual allele calling were performed as described by Hall and Nanthakumar (1997) and Idury and Cardon (1997). Genotype errors as a result of non-Mendelian segregation in pedigrees were detected and corrected as described by Hall and Nanthakumar (1997).

To facilitate inclusion of markers from different genetic maps (e.g., CEPH and the Cooperative Human Linkage Center), marker order and distances were calculated with genotype data from the 268 pedigrees. Marker order did not change with respect to the CEPH reference genetic maps. Compared with the CEPH maps,

intermarker distances varied by ⩽3 cM. On average, there were 726 informative meioses for each marker, although most meioses were phase-unknown, because few grandparents were available for genotyping in this family collection (the average number of phase-known meioses per marker was 7). Genetic maps for each chromosome were constructed with the automated mapping program MULTIMAP (version 2.0; Matise et al. 1994). The resulting distances between markers, determined by the Kosambi map function, are given in centimorgans.

### Statistical Analysis

Genetic analyses were conducted with the two standard diagnostic categories CD and UC, as described. A third category, ALL, contains CD/CD, UC/UC, and CD/UC (mixed) affected sib pairs (ASP). The ALL category therefore represents IBD as a single phenotype for analysis. Allele frequencies for each marker were calculated from the cohort genotype data with all individuals. Each of the 358 markers in the genome scan was analyzed, with two-point and multipoint nonparametric allele sharing tests in affected sibling pairs, by use of MAP-MAKER/SIBS with the "weighted pairs" option (Kruglyak et al. 1995). For multipoint analysis, LOD scores were computed at 1-cM intervals along each chromosome. The mean information content across the entire scan was 69%.

Power analyses were performed to determine the likelihood of detecting linkage under various gene effect sizes, with sample sizes corresponding to the three phenotype categories in this study. The methods used to determine the estimated power were the same as those described by Risch (1990). These power calculations assume fully informative matings. Because the average heterozygosity of our markers was ~75%, and complete parental information is not available for all families, the actual power to detect linkage in this study will not reach the values given in table 2. In addition, because markers in this study were spaced at ~10-cM intervals, the power to detect linkage was calculated at a recombination fraction of .05 between marker and disease locus (the average maximum distance between a potential disease locus to a marker locus). These power calculations are shown in table 2.

### Results

All families in this study were genotyped with a total of 358 microsatellite markers, spanning the genome at an average resolution of 9.4 cM. Nonparametric linkage analysis of the entire sample (ALL) was performed, as well as of the two distinct phenotypes of CD and UC. Chromosomal regions with maximum LOD scores ($Z_{max}$)⩾1.5, in any of the three groups, are shown in

**Table 2**

**Power Estimates for Detecting Linkage at $Z_{max}$ Thresholds**

| $Z_{max}$ THRESHOLD | λ = 2 | | | λ = 3 | | |
|---|---|---|---|---|---|---|
| | UC | CD | ALL | UC | CD | ALL |
| 1.5 | .56 | .71 | .98 | .90 | .97 | .99 |
| 2 | .36 | .55 | .96 | .76 | .92 | .99 |
| 3 | .12 | .29 | .85 | .44 | .77 | .99 |

NOTE.—Power estimates for detecting linkage at $Z_{max}$ thresholds of 1.5, 2, and 3 for the sample investigated. Full information content and a recombination fraction between 0.05 marker and disease locus were assumed.

table 3, along with the two-point results from the respective markers closest to the linkage peak. A $Z_{max}$ of 1.5 corresponds to an approximate *P* value of .01 and is considered a cutoff for suggestive evidence of linkage. Linkages on chromosomes 12 and 16, described elsewhere, have been confirmed in this sample, and the linkage on chromosome 4 has been extended (table 3). Suggestive evidence for linkage was observed on chromosomes 1, 6, 10, and 22, with LOD scores of 2.08, 2.07, 2.30, and 1.52, respectively. The linkage evidence on chromosome 1q corresponds in location to the observation reported by Cho et al. (1998) for the CD phenotype in their study. A $Z_{max}$ of 1.71 was observed on chromosome X for UC. The strongest evidence for linkage across the genome is seen on chromosome 10, for CD, on chromosome X, for UC, and on chromosome 1, for the combined phenotype of IBD (ALL). No significant linkage results were observed when CD/UC or mixed pairs were analyzed separately (data not shown). Multipoint $Z_{max}$ curves for CD, UC, and ALL IBD pairs, for all chromosomes, are shown in figure 1.

The family collection has a 1.5-fold excess of CD over the UC phenotype (table 1). These two phenotypes contribute, to different degrees, to the linkage regions seen in this study. The UC phenotype contributes most strongly to the linkages on chromosomes 1, 4, and one of the X-chromosome peaks. The CD phenotype dominates the linkages on chromosomes 10, 12, and 16. A more equal relationship is seen for the peaks on chromosomes 6 and 22 (table 3 and fig. 1).

### Discussion

To facilitate identification of IBD loci and enhance our overall understanding of the genetic basis of IBD, we sampled 268 families with IBD, yielding a total of 353 affected sibling pairs, and examined this population using two-point and multipoint linkage analyses. This cohort represents the largest IBD ASP collection reported to date. In addition to providing substantial power to detect IBD susceptibility loci, this sample includes 114 UC ASPs, providing an opportunity to identify UC-spe-

**Table 3**

**LOD Scores and Loci for IBD Linkage Regions**

| | | MULTIPOINT PEAK | | | | TWO-POINT FLANKING MARKERS | | | |
|---|---|---|---|---|---|---|---|---|---|
| CHROMOSOME | PHENOTYPE CATEGORY | Position (cM)[a] | $Z_{max}$ | Average Sharing at Peak | $P$ Values[b] | MARKER | CD $Z_{max}$ | UC $Z_{max}$ | ALL $Z_{max}$ |
| 1 | ALL | 242 | 2.08 | .59 | .0044 | D1S2670 | .36 | .82 | 1.0 |
| | | | | | | D1S2682 | .79 | 1.22 | 1.43 |
| 4 | UC | 126 | 1.56 | .59 | .009 | D4S1575 | .00 | .69 | .06 |
| | | | | | | D4S424 | .00 | 1.15 | .00 |
| 6 | ALL | 34 | 2.07 | .57 | .0028 | D6S289 | .49 | .51 | 1.37 |
| | | | | | | D6S276 | .53 | 1.49 | 2.05 |
| 12 | CD | 67 | 1.82 | .61 | .0016 | D12S303 | 2.15 | .92 | .98 |
| | | | | | | D12S326 | 1.30 | .10 | .45 |
| 16 | CD | 25 | 1.71 | .56 | .0026 | D16S409 | 1.12 | .04 | .74 |
| | | | | | | D16S411 | 1.56 | .10 | 1.49 |
| 10 | CD | 46 | 2.30 | .60 | .0014 | D10S548 | 1.17 | .00 | .32 |
| | | | | | | D10S197 | .95 | .12 | .49 |
| 22 | ALL | 14 | 1.52 | .56 | .0038 | D22S315 | .18 | .89 | .88 |
| | | | | | | D22S421 | .45 | .45 | .88 |
| X | ALL | 37 | 1.59 | .68 (brother-brother) | .007 | DXS1202 | 1.27 | .43 | 1.96 |
| | | | | | | DXS1214 | 1.19 | .03 | .63 |
| X | UC | 132 | 1.71 | .83 (sister-sister) | .005 | DXS1001 | .23 | .83 | .61 |
| | | | | | | DXS1047 | .11 | .79 | .00 |

NOTE.—Loci with multipoint $Z_{max}>1.5$ in either the total IBD (ALL), CD, or UC samples were included. Two-point $Z_{max}$ for the closest markers to the multipoint peak are given for the total and sample subsets. The nominal $P$ values shown are not corrected for multiple testing.

[a] Marker distances were calculated from the families analyzed with the program MULTIMAP (Matise et al. 1994). Map distances are given in Kosambi centimorgans from the p-telomeric marker of the chromosome (for chromosomes 1, 4, 6, 12, 16, 10, 22, and X markers: D1S468, D4S412, D6S344, D10S249, D12S99, D16S407, D22S420, and DXS1060, respectively).

[b] Probability values for autosomal $Z_{max}$ were determined by Monte Carlo simulation of the genotypes in the families under analysis, in which all allele frequencies, familial relationships, phenotypic data, and missing genotype patterns were preserved. Probability values shown thus represent the proportion of times that $Z_{max}$ values greater than or equal to the observed statistic were observed in the simulations. The simulations were conducted 5,000 times for each $Z_{max}$. Complete genotype data for the markers on chromosome 12 were available for 162, 114, and 353 affected sibling pairs for UC, CD, and all families combined, respectively. The $P$ values for the X chromosome were calculated by converting the LOD scores to a $\chi^2$ statistic.

cific loci. Genomewide analyses of this population, with average marker spacing of <10 cM, has enabled identification of several new IBD susceptibility regions and provided important replication data supporting previously identified IBD loci. Evidence indicating IBD susceptibility loci was observed on chromosomes 1, 4, 6, 10, 12, 16, 22, and X (table 3).

New possible IBD predisposition regions on chromosomes 1, 10, and 22 have been identified in the present study. The susceptibility region on chromosome 10 is defined by the anonymous markers D10S547 and D10S20 and is supported by a multipoint $Z_{max}$ of 2.30 and peak average allele sharing of .60, when analyzed for the CD phenotype. A second interesting region is observed on chromosome 22 and is defined by markers D22S420 and D22S280. This region is supported by a multipoint $Z_{max}$ of 1.52, defined by analysis of all IBD ASPs in the cohort. Previous IBD genome scans provided suggestive evidence for a locus on chromosome 1. In the present study, a linkage maximum is observed on the distal portion of chromosome 1q. This locus is located ~100 cM and ~160 cM from the regions previously

implicated by Hugot et al. (1996) and Cho et al. (1998), respectively. These data suggest a new susceptibility locus for IBD on chromosome 1. There was nominal evidence of linkage on 1q in the Cho et al. (1998) paper, which might correspond to the data observed in this study. The importance of these newly identified IBD loci to the determination of the overall genetic risk for IBD will need to be supported by replication studies in additional populations.

Evidence of IBD linkage to the major histocompatibility complex (MHC) region of chromosome 6 was also observed in this sample. This finding is particularly interesting given that numerous associations with individual human leukocyte antigen (HLA) region genes, including class I (Gleeson et al. 1972; van den Berg Loonen et al. 1977; Purrmann et al. 1985; Biemond et al. 1986), class II (Fujita et al. 1984; Toyoda et al. 1993; Nakajima et al. 1995), and TNF-$\alpha$ alleles (Plevy et al. 1996; Bouma et al. 1998), have been described. The association data for HLA and TNF-$\alpha$ are not conclusive (Russell et al. 1975; Delpre et al. 1980; Smolen et al. 1982; Satsangi et al. 1996c). Questions regarding the significance of an
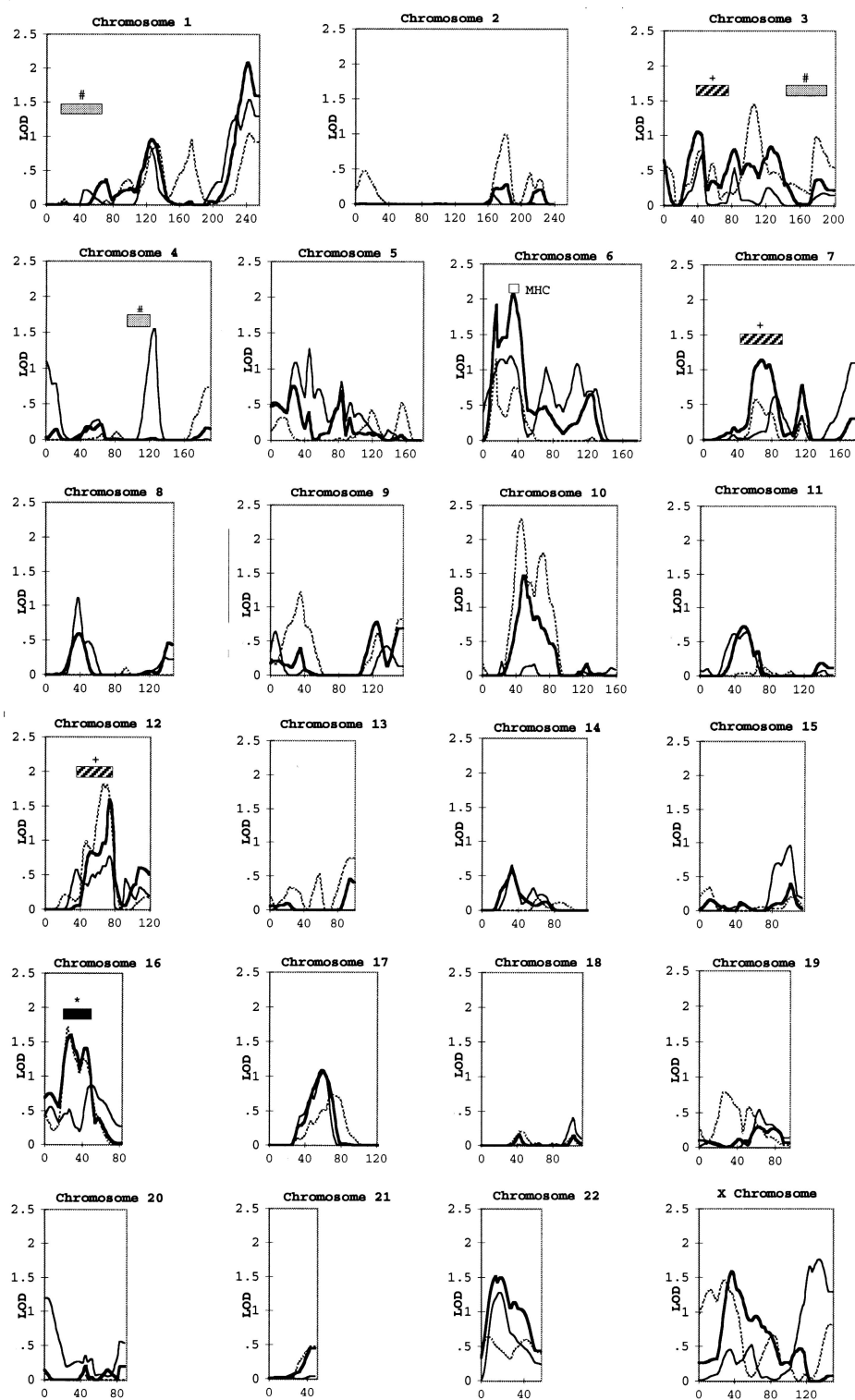
**Figure 1** Multipoint $Z_{max}$ curves for all chromosomes are shown. Multipoint analyses were done with the MAPMAKER/SIBS program. Results for CD (dashed line), UC (thin solid line), and all pairs (ALL, thick solid line) are shown. Genetic distances between markers were estimated from the data set. The reported regions of linkage from previous scans are denoted with an asterisk (*), a plus sign (+) and a pound sign (#), for the studies by Hugot et al. (1996), Satsangi et al. (1996b) and Cho et al. (1998), respectively.

IBD risk factor on chromosome 6 stem in part from the lack of linkage evidence implicating this region (Hugot et al. 1994; Naom et al. 1996). Suggestive evidence for linkage to the HLA region of chromosome 6 is now provided by the present study. Recent association studies have suggested a role for HLA in susceptibility to UC (Bouma et al. 1997; Roussomoustakaki et al. 1997; Perri et al. 1998; Uyar et al. 1998) and CD (Forcione et al. 1996). The association findings would be consistent with the contribution of UC and CD families to the chromosome 6 linkage, in the present study. The present data sets are insufficient to implicate HLA alleles as the only genetic risk factor in the chromosome 6p linkage region. As discussed below, there are a number of immunoregulatory genes in this region that may contribute to the observed phenotypes. In summary, the observation of evidence for linkage, coupled with the numerous association findings, suggests that a susceptibility gene for IBD does exist in the HLA region of chromosome 6.

An increased incidence of IBD in patients with Ullrich-Turner syndrome has been observed, suggesting a possible link between these disorders ( Price 1979; Arulananantham et al. 1980; Kohler and Grant 1981; Knudtzon et al. 1988; Knudtzon and Svane 1988; Scarpa et al. 1996). This hypothesis is supported by evidence of X chromosome linkages observed in this study. Interestingly, the X-chromosome linkage curve has two peak regions, with UC defining a linkage interval on distal Xq (multipoint $Z_{max} = 1.71$), and ALL IBD providing evidence for linkage to distal Xp (multipoint $Z_{max} = 1.59$). Elucidation of the role of the X chromosome in IBD, and possible implications for Ullrich-Turner syndrome, await further investigation.

IBD susceptibility regions located on chromosomes 3, 7, 12, and 16 have been identified in previous genomewide linkage scans (Hugot et al. 1996; Satsangi et al. 1996b). The loci on chromosomes 12 and 16 are supported by results from the present study. Additional IBD susceptibility loci on chromosomes 1q, 3q, and 4q have been reported (Cho et al. 1998). The investigators used a methodology that exploits allele-sharing information in ASPs ($N = 151$), as well as distant relative pairs ($n = 146$). In addition to the methodologic differences, an ethnically more diverse population sample was analyzed. In our population, we also observe evidence for linkage to chromosome 4q, with the peak location ~20 cM more distal when compared with the Marshfield genetic map (Marshfield Center for Medical Genetics database). The discrepancy, with regard to peak location, is not unexpected for a complex disease (Kruglyak and Lander 1996). It is therefore likely that both linkages indicate the same chromosome 4 susceptibility locus.

The power to detect true susceptibility regions by means of nonparametric linkage analyses is highly dependent on the size of the population being tested and the locus-specific effect. If we take into consderation a LOD score threshold of 2 for a primary genome scan analysis, our sample size exceeds the 80% power typically needed for genes with a small to moderate effect ($\lambda_s = 2$), for the combined ALL IBD phenotype (table 2). In this study, linkages defined by the UC and CD phenotypes exhibit different degrees of statistical significance. This may indicate potential genetic differences between the two phenotypes. Interpretation of these data is complicated, however, by the following factors: (1) since CD families constitute two-thirds of the analyzed sample, there is a power bias in favor of CD; (2) the clinical overlap between CD and UC may confound efforts to genetically distinguish between the two phenotypes (Podolsky 1991); and (3) the stochastic nature of the family sampling process can lead to variations in LOD scores, without significant differences in the underlying disease model (Suarez et al. 1994; Hampe et al., in press). UC, although approximately twice as prevalent as CD in northern European populations (Shivananda et al. 1996), has been studied in significant numbers in only one genomewide analysis (Satsangi et al. 1996b), which included 30 affected sibling pairs. In the present study, with 114 UC affected sib pairs, we establish replication of UC linkage to chromosome 12 and provide suggestive evidence for new UC regions on chromosomes 1, 4, and X. Although an important clinical issue, it is likely that true differentiation between CD and UC will not be possible until after the discovery of the variants underlying genetic predisposition to IBD.

The pathophysiology of IBD is characterized by a dysregulated immune response of the intestinal mucosa. Although the IBD susceptibility regions are large, it is useful to note that many interesting candidate genes are located in these regions. The chromosome 6 IBD interval contains a series of important immune-response genes, including the MHC, TNF-$\alpha$, and TNF-$\beta$ (Gleeson et al. 1972; van den Berg Loonen et al. 1977; Plevy et al. 1996); several complement factors that are thought to be important inflammatory effectors (Carroll 1998); and the NFKBIL1 gene (Baeuerle 1998). Integrins have key roles in cellular adherence and are participants in inflammatory and immune responses. The integrin-$\beta$1 gene, located on chromosome 10, and the integrin-$\beta$7 and $\alpha$5, genes on chromosome 12, are putative candidates for IBD (Gahmberg et al. 1998). Cytokines and their receptors are critical in proliferation and differentiation of multiple cell types and are thought to be involved in the pathogenesis of IBD (Schreiber et al. 1995; Rogler and Andus 1998). The interleukin-4 receptor and interleukin-2 genes are located within the chromosome 16 and chromosome 4 linkage regions. Evidence from a large association study indicates that the interferon-$\gamma$ gene is not likely to be the IBD susceptibility gene in the chromosome 12 linkage region (Hampe et

al. 1999). Additional positional candidates for IBD include the TGF-$\beta$2 and TGF-$\beta$4 genes on chromosome 1q, which are involved in wound healing and tissue restoration (Rogler and Andus 1998; Schmid et al. 1998), and the ubiquitin-conjugating enzyme E2G, which is likely to be important in the processing of antigens (Hochstrasser 1996). Direct investigations into a possible role of these genes in the cause of IBD are ongoing. The autosomal linkages observed in this study overlap with regions implicated in other autoimmune disorders: the chromosome 12 linkage overlaps with regions implicated in asthma and multiple sclerosis, and the chromosome 16 linkage overlaps with a locus for insulin-dependent diabetes mellitus, asthma, and experimental autoimmune encephalitis (Becker et al. 1998). These observations may indicate common etiologic pathways involved in the defective immunoregulation observed in these disorders.

In conclusion, we have identified multiple potential novel linkages for IBD and provided important replication data for several previously identified IBD linkages. These findings increase our overall understanding of the genetic basis of IBD, may be useful for development of genetic tests for differentiating among clinical IBD phenotypes, and will ultimately facilitate identification of the genes and molecular variants that cause this disease.

## Acknowledgments

## Electronic Database information

Accession numbers and URLs for data in this article are as follows:

Cooperative Human Linkage Center, http://www.chlc.org (for markers used)
Généthon, http://www.genethon.fr (for CEPH markers used)
Marshfield Center for Medical Genetics, http://www.marshmed.org/genetics/ (for genetic maps used)
MultiMap home page, http://linkage.rockefeller.edu/multimap (for MULTIMAP)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.gov/Omim (for IBD [MIM 601458], CD [MIM 266600], and UC [MIM 191390])
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www.genome.wi.mit.edu/ftp/distribution/software (for MAPMAKER/SIBS)

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