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Report

The *IBD2* Locus Shows Linkage Heterogeneity between Ulcerative Colitis and Crohn Disease

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The *IBD2* locus on chromosome 12 has been linked to both Crohn disease (CD) and ulcerative colitis (UC) but has not been detected in some CD-dominated data sets. In the present study, we genotyped 581 relative pairs with inflammatory bowel disease (252 from CD-only families, 138 from UC-only families, and 191 from mixed families containing cases of both CD and UC), using 12 markers spanning the *IBD2* locus. A GENEHUNTER-PLUS multipoint LOD score of 3.91 was detected for pairs from UC-only families, compared with 1.66 for CD-only and 1.29 for mixed families. The difference between the LOD scores for UC and CD was significant in two different tests for heterogeneity ($P = .0057$ for one test and $P = .0375$ for the other). *IBD2* thus appears to make a major contribution to UC susceptibility but to have only a relatively minor effect with regard to CD, for which there may be substantially more locus heterogeneity.

Crohn disease (CD [MIM 266600]) and ulcerative colitis (UC [MIM 191390]), the two common forms of inflammatory bowel disease (IBD), have a combined prevalence, in populations of northern European origin, of 150–200/100,000. Evidence for a strong genetic contribution to IBD comes from twin studies, which demonstrate a substantially higher rate of disease concordance in MZ compared with DZ twins, and from family studies, which demonstrate consistently high λ_s scores (sibling risk/population prevalence). This is particularly true for CD (λ_s = 20–35; twin concordance MZ:DZ = 36%:12%) and, to a lesser extent, for UC (λ_s = 8–15; twin concordance MZ:DZ = 12%:3%) (Tysk et al. 1988; Probert et al. 1993; Satsangi et al. 1994; Subhani et al. 1998).

Although genetic susceptibility is clearly important, the inheritance of IBD is complex. Furthermore, the etiologic basis of the relationship between CD and UC is as yet unexplained. Some phenotypic features are shared; up to 10% of cases are classified as indeterminate; and the two forms of IBD run together within a single pedigree in ~30% of multiply affected families (Kirsner 1973; Satsangi et al. 1994). However, there are also some notable epidemiological differences—for example, in sibling recurrence risk and in twin concordance rates (Tysk et al. 1988; Probert et al. 1993; Subhani et al. 1998)—and CD and UC remain distinct clinical entities with separate patterns of behavior. The genetic model that best fits is therefore one in which CD and UC are related polygenic diseases that may share some susceptibility loci but differ at others.

Genome scanning in IBD has established a number of replicated regions of linkage, including loci on chromosomes 3, 6, 12, 14, and 16. The candidate region on chromosome 12 (the *IBD2* locus [MIM 601458]) has been reported for both CD and UC (Satsangi et al. 1996; Akolkar et al. 1998; Curran et al. 1998; Duerr et al. 1998; Hampe et al. 1999; Ma et al. 1999), whereas the region on chromosome 16 (the *IBD1* locus [MIM 266600]) appears to be linked exclusively to CD (Hugot et al. 1996; Ohmen et al. 1996; Parkes et al. 1996; Brant et al. 1998; Cavanaugh et al. 1998; Cho et al. 1998; Curran et al. 1998; Annese et al. 1999; Hampe et al. 1999; IBD Genetics Consortium 2000).

Although the chromosome 12 linkage has been rep-

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licated in a number of data sets (Satsangi et al. 1996; Akolkar et al. 1998; Curran et al. 1998; Duerr et al. 1998; Hampe et al. 1999; Ma et al. 1999), it has not been found in all, and three studies claimed to exclude this region for a locus-specific $\lambda_s > 2$ (Brant et al. 1998; Rioux et al. 1998; Vermeire et al. 2000). There are many precedents for failure to replicate linkages in complex diseases—and many possible explanations, particularly relating to power (Suarez et al. 1994; Mandal et al. 1999), but we were struck by the fact that the studies that have failed to detect linkage between IBD and the chromosome 12 locus have contained few relative pairs with UC. The aim of the current study, therefore, was to evaluate further the *IBD2* locus in a large panel of multiply affected families and, specifically, to determine its relative contribution to CD susceptibility and UC susceptibility.

Ethical approval for this work was given by the Central Oxford Research and Ethics Committee and the University of Pittsburgh Institutional Review Board for Biomedical Research. The panel of U.K. and U.S. families studied are described in table 1. A total of 581 IBD-affected relative pairs were genotyped, including 396 affected sib pairs. There were 252 affected relative pairs from CD-only families, 138 pairs from UC-only families, and 191 pairs from families in which cases of UC and CD coexisted ("mixed" families). Case notes were reviewed to confirm the diagnoses. All individuals in the panel were white European in origin. Ashkenazi Jewish ethnicity was reported in 43 (11.7%) of the 367 families. The U.K. and U.S. panels each included families used and described in earlier studies, in addition to families more recently recruited, particularly with regard to the U.S. panel (Satsangi et al. 1996; Duerr et al. 1998).

Twelve markers spanning the peak of the chromosome 12 candidate interval, as defined in previous reports by both our group and others (Satsangi et al. 1996; Akolkar et al. 1998; Curran et al. 1998; Duerr et al. 1998; Hampe et al. 1999; Ma et al. 1999), were studied in the combined U.K./U.S. panel. Each microsatellite was amplified by PCR using fluorescence-labeled oligoprimers. The fluorescently labeled PCR amplimers were electrophoresed and detected on ABI 373 and 377 DNA sequencers (Applied Biosystems) and were genotyped by either GENESCAN/GENOTYPER (Applied Biosystems) (U.K. panel) or TrueAllele (Cybergenetics) (U.S. panel) software. A control DNA, CEPH 1347-02, was run on each genotyping gel, and the results were used to standardize allele calls between gels and between the two genotyping labs. Genotyping data were checked for Mendelian inconsistencies, by PEDCHECK (O'Connell and Weeks 1998 [also see the University of Pittsburgh Division of Statistical Genetics Web page]).

Marker order was determined by radiation-hybrid mapping using Genebridge 4 and Stanford TNG panels (both from Research Genetics). Map distances were calculated by the ILINK function of the VITESSE package (O'Connell and Weeks 1995 [also see the University of Pittsburgh Division of Statistical Genetics Web page]), on the basis of genotyping data from the family panel and of calculation of multipoint distances between overlapping sets of four markers.

Single- and multipoint linkage analyses were performed by GENEHUNTER-PLUS (Kong and Cox 1997 [also see those authors' GENEHUNTER-PLUS Web page, for GENEHUNTER-PLUS version 1.2]). This modified version of the GENEHUNTER program (Kruglyak et al. 1996) uses a simple one-parameter linear model to compute a nonparametric LOD score, analogous to a parametric LOD score, which can be used for

Table 1

Number of Families and Number of Genotyped Affected Relative Pairs

CATEGORY	All IBD	CD Only	Mixed	UC Only
U.K. families	171	79	30	62
Genotyped affected relative pairs	222	100	45	77
Sib pairs	199	93	35	71
Half-sib pairs	1	0	0	1
Avuncular pairs	18	6	7	5
Grandparent-grandchild pairs	1	0	1	0
First-cousin pairs	3	1	2	0
U.S. families	196	86	73	37
Genotyped affected relative pairs	359	152	146	61
Sib pairs	197	106	59	32
Half-sib pairs	6	5	1	0
Avuncular pairs	67	23	32	12
Grandparent-grandchild pairs	4	0	2	2
First-cousin pairs	46	12	23	11
Other, more distant pairs	39	6	29	4
Total families	367	165	103	99
Total genotyped affected relative pairs	581	252	191	138

construction of support regions and for comparison of loci. Our analysis used the S_{pairs} statistic, which measures identity-by-descent allele sharing between all pairs of affected relatives. The panel was considered as a whole (IBD overall) and then was divided into UC-only, CD-only, and mixed family subsets.

The results of single-point linkage analysis of the 12 markers studied are presented in table 2. The highest single-point LOD score for IBD overall occurred at D12S83 (LOD score 5.26). Most of the support for linkage comes from the 138 affected relative pairs from UC-only families, in whom the peak single-point LOD score was 3.78 at D12S1586, compared with a peak LOD score of 1.59 at D12S90 in the 252 affected pairs from CD-only families and a peak LOD score of 2.09 at D12S83 in the 191 affected pairs from mixed families.

Results of the multipoint linkage analysis are presented in figure 1. The peak GENEHUNTER-PLUS LOD score for IBD overall was 5.19. A maximum LOD score of 3.91 was observed in the UC-only families, compared with 1.66 in the CD-only families and 1.29 in the mixed families. The discrepancy of 7 cM between the peaks of the linkage curves for UC and CD, reflected in the two peaks of the IBD curve, probably reflects the limited resolution of haplotype-sharing methods of linkage analysis for fine mapping in polygenic diseases (Kruglyak and Lander 1996). However, it is also possible that there is more than one IBD-susceptibility gene in this region, with these exerting differential effects in UC and CD. A precedent for detection of more than one gene per linkage interval comes from fine mapping in mouse models of type 1 diabetes (Podolin et al. 1998).

To formally test for heterogeneity between the UC-only and CD-only families, two simulation studies were employed. In the first simulation study, we examined the probability of obtaining the GENEHUNTER-PLUS LOD-score difference that we observed under the null hypothesis of no linkage. For the second simulation study, we examined the probability of randomly dividing our sample into two groups similar in size to our UC-only and CD-only families and achieving a similarly high difference in GENEHUNTER-PLUS LOD scores. Taken together, these two studies show that our division of families is unique—and that the LOD-score difference that we observed would not be obtained very often by chance.

For the first simulation study, we used Morton's M test (Morton 1956):

$$X = 2\ln(10)\left[\sum_i Z_i(\hat{\theta}_i) - Z(\hat{\theta})\right] .$$

This test divides a sample into n groups and then compares the LOD scores in the individual groups versus the combined LOD score in the entire sample. In the equation above, $Z_i(\hat{\theta}_i)$ is the total LOD score for the families in the ith class ($i = 1, \ldots, n$), and $\hat{\theta}_i$ is the maximum-likelihood estimate of the recombination fraction in the ith class. The null hypothesis of no heterogeneity between groups would be represented by the case in which the sum of the individual groups' LOD scores would be exactly equal to the combined sample LOD score (i.e., $[\Sigma_i Z_i(\hat{\theta}_i) - Z(\hat{\theta})] = 0$). We simulated the distribution of this statistic to determine the P value associated with our observed statistic value. In the computer simulation, random genotype data for all the markers in the region were generated 10,000 times each for the group of CD-only families and for the group of UC-only families, and, each time, Morton's M test was

Table 2

Single-Point GENEHUNTER-PLUS LOD Scores for 12 Markers Studied in the Combined U.K./U.S. Panel

Map Position[a] (cM)	Microsatellite Locus	Heterozygosity (%)	No. of Alleles Observed	GENEHUNTER-PLUS Single-Point LOD Score for			
				All IBD	CD Only	Mixed	UC Only
0.0	D12S85	68.2	13	2.31	.28	1.23	1.13
5.3	D12S368	82.5	9	2.62	.38	1.59	1.11
6.8	D12S1586	84.6	13	3.11	.25	.52	3.78
8.1	D12S1724	78.5	13	5.21	1.52	1.45	2.49
10.9	D12S90	76.2	11	4.20	1.59	1.23	1.41
11.6	D12S305	66.8	10	2.09	.54	.88	.80
12.5	D12S1700	78.7	14	2.63	.30	1.57	1.43
13.1	D12S1056	70.0	6	3.25	.97	.71	1.87
13.6	D12S1662	71.6	9	4.41	1.01	.77	3.48
14.4	D12S83	77.4	13	5.26	1.35	2.09	2.05
15.1	D12S1655	70.4	9	2.02	.56	.65	.95
25.1	D12S335	80.7	14	1.18	.01	.12	2.58

[a] Marker order was determined by radiation-hybrid mapping, and genetic distance was computed by the VITESSE package.

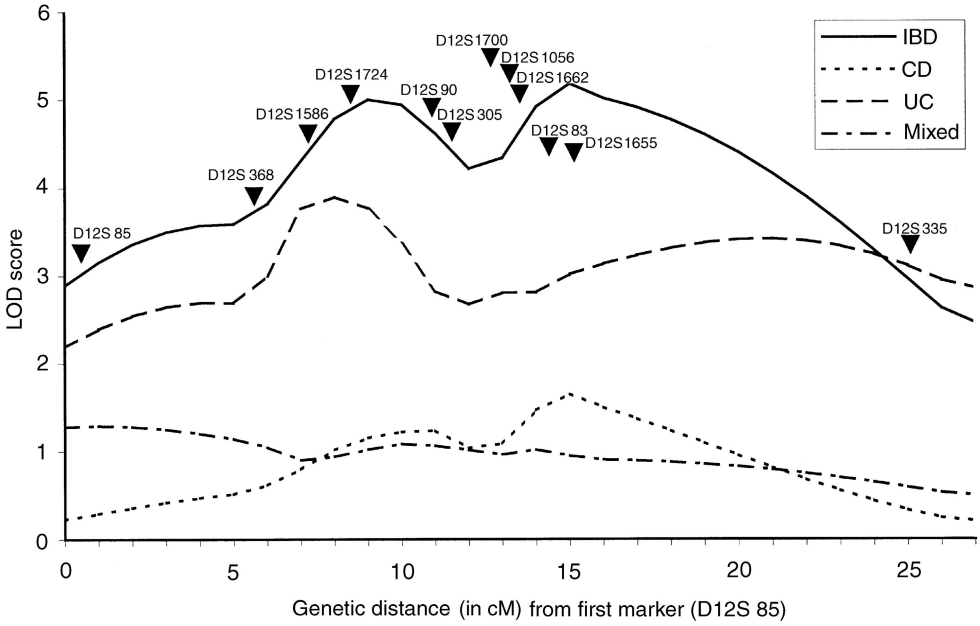

Figure 1 Results of multipoint nonparametric linkage analysis for markers across the 25-cM candidate interval on chromosome 12. Results are given for IBD overall and for subsets containing UC-only, CD-only, and mixed families. LOD scores derived from GENEHUNTER-PLUS (*Y*-axis) are plotted against distance (in cM) from D12S85.

performed using the GENEHUNTER-PLUS LOD scores computed on the basis of the simulated data. The *P* value for our observed heterogeneity statistic value was determined by counting how often the simulated data produced a heterogeneity statistic value as high as our observed heterogeneity statistic value. The simulations showed that the heterogeneity statistic value that we observed between the UC-only families and the CD-only families is unlikely to occur by chance ($P = .0057$) and that it therefore represents true evidence of heterogeneity between these two sets of families.

The second simulation study that we performed looked at the significance of the division of samples. For this study, we compared the distribution of LOD scores obtained when the available families (367) were randomly split into two groups of sizes similar to those of the UC-only and CD-only groups (99 and 165 families, respectively). To do this, we randomly selected (without replacement) 99 pedigrees from our sample and then another 165 pedigrees and then calculated the maximum GENEHUNTER-PLUS LOD scores for the new samples. This procedure was repeated 10,000 times, to generate a distribution of GENEHUNTER-PLUS LOD-score differences. A difference greater than or equal to our observed UC-CD LOD-score difference (2.25) was observed only 375 times in 10,000 replications ($P = .0375$). Together, then, these two simulation studies indicate that we have significant heterogeneity in our sample and that clinical diagnosis is a significant factor influencing the LOD-score difference.

With the LOD score of 3.91 for UC-only families, the results of this study provide the first evidence of a "significant" linkage result for UC when the established genomewide criteria of Lander and Kruglyak (1995) are used. The multipoint LOD score of 5.19 for IBD is certainly also respectable in the context of a polygenic disease. Although there is likely to be some positive bias in these results, given that both the U.K. and the U.S. panels contained affected relative pairs known to show increased haplotype sharing in this region, it is also true that the number of affected relative pairs has expanded by a total of 39% beyond those reported originally, and the intuitive expectation that LOD scores from different data sets should be additive can be confounded by heterogeneity in the study populations.

Of interest was the impact that increasing the size of the data set had on the LOD scores, both for IBD overall and for the CD and UC subgroups. In the original U.K. data set (208 affected relative pairs), peak multipoint LOD scores were 3.87 for IBD, 1.08 for CD, and 1.54 for UC (M.P. and D.P.J., unpublished data), and in the U.S. data set (208 affected relative pairs) they were 2.79 for IBD, 1.79 for CD, and 1.82 for UC (Duerr et al. 1998); for the two expanded data sets combined (581 affected relative pairs) the peak multipoint LOD scores are 5.19 for IBD, 1.66 for CD, and 3.91 for UC. Thus, although the evidence for linkage of this region to IBD overall has increased, it can be seen that this is predominantly due to an increase in the strength of linkage to UC, with the LOD score for CD essentially unchanged

despite the increase in genotyped families. This suggests relatively more heterogeneity within the CD population, at least with regard to the *IBD2* locus, as well as a stronger contribution of this region to UC susceptibility. The latter is corroborated both by the stronger evidence for linkage to UC compared with that to CD, despite the substantially smaller size of the UC group (138 affected relative pairs from UC-only families, compared with 252 affected relative pairs from CD-only families), and, in particular, by the fact that the difference between the LOD score for UC and that for CD is significant in the heterogeneity tests.

The apparently stronger effect that we have observed for UC is likely to have an impact on interpretation of future linkage reports in this region and might, in part, explain the failure of some (CD-dominated) data sets to show significant linkage at markers within the chromosome 12 candidate interval (Brant et al. 1998; Rioux et al. 1998; Vermeire et al. 2000). If the evidence for linkage heterogeneity between the disease subgroups at *IBD2* is indicating a major gene effect for UC but a relatively minor one for CD, and if there truly is more linkage heterogeneity at *IBD2* within the CD population, then clearly this linkage will be more difficult to detect in panels of families containing a majority of CD relative pairs.

The picture emerging for the *IBD2* locus is therefore one of a major contribution with regard to UC susceptibility but probably a relatively minor effect for CD—with the likelihood of substantially more heterogeneity, with regard to *IBD2,* for CD. Given the findings of the current study, attempts at fine mapping the *IBD2* locus should probably focus, at least in the first instance, on individuals and families with UC. The increasing availability of sequence data, single-nucleotide polymorphisms, and information regarding positional candidate genes, together with the accumulation of ever larger IBD subsets, can only help this process—and, thereby, help us to understand the contribution that this locus makes to the pathogenesis of IBD.

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Electronic-Database Information

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

GENEHUNTER-PLUS Web page, ftp://galton.uchicago.edu/pub/kong (for GENEHUNTER-PLUS version 1.2)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for CD [MIM 266600], UC [MIM 191390], *IBD1* [MIM 266600], and *IBD2* [MIM 601458])

University of Pittsburgh Division of Statistical Genetics Web page, http://watson.hgen.pitt.edu/pub/register (for PEDCHECK and VITESSE programs)

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