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High-Density Genome Scan in Crohn Disease Shows Confirmed Linkage to Chromosome 14q11-12

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Epidemiological studies have shown that genetic factors contribute to the pathogenesis of the idiopathic inflammatory bowel diseases (IBD), Crohn disease (CD) and ulcerative colitis (UC). Recent genome scans and replication studies have identified replicated linkage between CD and a locus on chromosome 16 (the *IBD1* locus), replicated linkage between IBD (especially UC) and a locus on chromosome 12q (the *IBD2* locus), and replicated linkage between IBD (especially CD) and a locus on chromosome 6p (the *IBD3* locus). Since the estimated locus-specific λ_s values for the regions of replicated linkage do not account for the overall λ_s in CD, and since the published genome scans in IBD show at least nominal evidence for linkage to regions on all but two chromosomes, we performed an independent genome scan using 751 microsatellite loci in 127 CD-affected relative pairs from 62 families. Single-point nonparametric linkage analysis using the GENEHUNTER-PLUS program shows evidence for linkage to the adjacent D14S261 and D14S283 loci on chromosome 14q11-12 (LOD = 3.00 and 1.70, respectively), and the maximal multipoint LOD score is observed at D14S261 (LOD = 3.60). In the multipoint analysis, nominal evidence for linkage ($P < .05$) is observed near D2S117 (LOD = 1.25), near D3S3045 (LOD = 1.31), between D7S40 and D7S648 (LOD = 0.91), and near D18S61 (LOD = 1.15). Our finding of significant linkage to D14S261 and the finding of suggestive linkage to the same locus in an independent study (multipoint LOD = 2.8) satisfies criteria for confirmed linkage, so we propose that the region of interest on chromosome 14q11-12 should be designated the *IBD4* locus.

Introduction

Crohn disease (CD) (MIM 266600) and ulcerative colitis (UC) (MIM 191390) are the major forms of idiopathic inflammatory bowel disease (IBD) (MIM 266600 and MIM 601458) that can usually be distinguished from each other on the basis of clinical parameters, but which also share clinical features and unknown etiology (Lashner 1995; Singleton 1995). The prevalence of IBD in Europe and North America is ~100-200 per 100,000 (Calkins and Mendelhoff 1995).

Greater rates of IBD in Ashkenazi Jews, familial aggregation of IBD, and a greater concordance for IBD in monozygotic than dizygotic twins indicate that there is a genetic contribution to the pathogenesis of IBD, with a stronger genetic influence in CD than in UC (Yang and Rotter 1994; Duerr 1996). The relative risk to siblings of affected individuals (λ_s) is 30–40 for CD and 10–20 for UC, and CD and UC also occur together in the same families with a greater frequency than would be expected by chance (Yang and Rotter 1994; Duerr 1996).

Although genetic factors clearly contribute to IBD susceptibility, the inheritance of IBD is not attributable to a single gene locus; CD and UC have complex genetics that involve incomplete penetrance and probably genetic heterogeneity and more than one susceptibility locus (Yang and Rotter 1994; Duerr 1996). Since both forms of IBD can coexist in single families with a frequency greater than expected by chance, CD and UC are likely to share some susceptibility genes, although there may be additional CD-specific and UC-specific genes (Yang and Rotter 1994; Duerr 1996). Recent genome scans and replication studies have identified replicated linkage between CD and a locus on chromosome 16 (the *IBD1* locus [MIM 266600]) (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*a*), replicated linkage between IBD (especially UC) and a locus on chromosome 12q (the *IBD2* locus [MIM 601458]) (Satsangi et al. 1996; Duerr et al. 1998; Curran et al. 1998; Akolkar et al. 1998; Hampe et al. 1999*a;* Ma et al. 1999), replicated linkage between IBD (especially

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CD) and a locus on chromosome 6p (the *IBD3* locus [MIM 604519]) (Hampe et al. 1999*a,* 1999*b;* Silverberg et al. 1999; Yang et al. 1999), and at least nominal evidence for linkage to regions on all but two chromosomes (Hugot et al. 1996; Satsangi et al. 1996; Cho et al. 1998; Hampe et al. 1999*a;* Ma et al. 1999). Since the estimated locus-specific λ_s values for the regions of replicated linkage do not account for the overall λ_s in CD, we aimed to find further support for linkage to other loci.

Material and Methods

Study Subjects

The study protocol was approved by the University of Pittsburgh Health Sciences Institutional Review Board. Sixty-two families containing 127 CD-affected relative pairs and 287 total study subjects were included in the genome scan. The CD-affected relative pairs included 94 sibling pairs, 4 half-sibling pairs, 19 avuncular pairs, and 10 other affected relative pairs as distant as first cousins once removed. Offspring of unavailable connecting relatives were recruited whenever possible to increase the probability of determining identity-by-descent allele/haplotype sharing in the affected relative pairs. Both parents, or one parent and at least two siblings, were included in the study for 76% of the nonfounder affecteds. All study subjects were interviewed to complete a demographic and clinical database, and consents for release of medical records to verify diagnoses were obtained from affected study subjects. In all but two families, there were no known cases of UC. In two families, we became aware of a relative with UC after we included the families in the genome scan (a trio of CD-affected siblings was found to have a first cousin with UC, and a CD-affected sibling pair was found to have a second cousin with UC). All study subjects were whites of European descent. Ashkenazi Jewish ethnicity was reported in eight of the 62 families.

Genotyping

We genotyped our study subjects at 395 microsatellite loci in the ABI PRISM Linkage Mapping Set Version 2 (PE Applied Biosystems). Five microsatellite loci in the ABI PRISM Linkage Mapping Set Version 2 were found to be problematic and were not included in the genome scan. Up to twelve fluorescent dye-labeled microsatellite polymerase chain reaction amplimers from single DNA samples were pooled together, heat denatured, and loaded into ABI 377 DNA Sequencers (PE Applied Biosystems) for GENESCAN data collection. The data were analyzed and alleles assigned using the TrueAllele software (Cybergenetics).

An additional 356 microsatellite loci in the Weber version 9 screening set were genotyped by the NHLBI Mammalian Genotyping Service at the Center for Medical Genetics in Marshfield, Wisconsin. The genetic spacing between the total of 751 microsatellite loci averaged 4.6 centimorgans (cM), according to comprehensive genetic maps of microsatellite loci by Broman et al. (1998).

Statistical Analyses

Mendelian inheritance was checked using the PedCheck program, which uses the individual's genotype information to check for parent-child inconsistencies and too many alleles in a sibship and then uses genotype elimination to find more subtle errors (O'Connell and Weeks 1998). Allele frequencies for each microsatellite locus were estimated by counting alleles in unrelated individuals, augmented by the addition of nontransmitted alleles derived from each nuclear family unit.

Single- and multipoint nonparametric linkage analyses were carried out by means of the "S_{pairs}" scoring function in the GENEHUNTER-PLUS modification of the GENEHUNTER package (Kruglyak et al. 1996; Kong and Cox 1997). GENEHUNTER-PLUS performs a likelihood-based, nonparametric analysis of allele and haplotype sharing in affected-relative pairs and computes a nonparametric LOD score (Kong and Cox 1997). The X-linked version of GENEHUNTER-PLUS was used for the chromosome X analyses. To reduce the potential for misspecification of marker order in the multipoint analyses, only those Weber version 9 markers that were $\geq$2 cM away from the nearest ABI marker were included in the multipoint analyses, giving a total of 588 microsatellite loci with an average genetic spacing of 5.9 cM in the multipoint analyses. We observed the guidelines for interpreting and reporting linkage results proposed by Lander and Kruglyak (Lander and Kruglyak 1995).

Results

Loci with single-point GENEHUNTER-PLUS *P* values < .05 are shown in table 1. The two microsatellite loci with the greatest single-point LOD scores are the adjacent D14S261 and D14S283 loci on chromosome 14q11-12 (LOD = 3.00 and 1.70, respectively). Nominal evidence for linkage is observed at two adjacent markers on chromosome 18q22 (D18S61 and ATA82B02).

A summary of the information content for each chromosome from the GENEHUNTER multipoint output is shown in table 2. The average information content across the genome is 0.74. This reflects the relatively high genotyping information from connecting relatives and the high density of genotyped genetic markers in our study. The GENEHUNTER-PLUS multipoint LOD score curves for chromosomes with nominal multipoint *P* values < .05 are shown in figure 1. The maximal multipoint LOD score in our genome scan is at D14S261 on chromosome 14q11 (LOD = 3.60). The

Table 1

Loci with Nominal Evidence for Linkage in GENEHUNTER-PLUS Single-Point Analyses

Chromosome	Position (cM)	Microsatellite	LOD	*P*
1	29.9	D1S1597	1.48	.0092
2	194.5	D2S117	1.30	.014
9	44.3	D9S1121	1.40	.011
9	147.9	D9S164	1.01	.031
12	0.0	D12S352	.91	.041
14	6.5	D14S261	3.00	.0002
14	13.9	D14S283	1.70	.0051
17	22.2	D17S974	.91	.041
18	105.0	D18S61	1.34	.013
18	106.8	ATA82B02	1.07	.026
19	9.8	D19S591	1.60	.0067
20	47.5	D20S477	1.16	.021

evidence for linkage at D14S261 is at the threshold for declaring significant linkage in a genome scan (Lander and Kruglyak 1995). The 1-LOD-unit support interval extends to 4 cM q-telomeric from D14S261, and *P* values < .05 are observed over a 13-cM region q-telomeric from D14S261. There are no other regions for which the Lander and Kruglyak criteria for declaring significant or suggestive linkage in a genome scan are satisfied (Lander and Kruglyak 1995). Nominal evidence for linkage with multipoint *P* values < .05 is present near D2S117 (LOD = 1.25), near D3S3045 (LOD = 1.31), between D7S40 and D7S648 (LOD = 0.91), and near D18S61 (LOD = 1.15).

Discussion

Our genome scan using 751 microsatellite loci in 127 CD-affected relative pairs has found strong evidence for linkage between CD and chromosome 14q11-12. The maximal linkage evidence in this region (multipoint LOD = 3.60 at D14S261) is at the threshold for declaring significant linkage in a genome scan (Lander and Kruglyak 1995). Recently, investigators from Cedars-Sinai/Parke Davis reported the results of a genome scan in 65 CD-affected sibling pairs (Ma et al. 1999). They found evidence suggestive of linkage (multipoint LOD = 2.8) to D14S261 (Ma et al. 1999). In addition, Cho et al. found nominal evidence for linkage to this general region of chromosome 14 in their subset of mixed families containing both CD- and UC-affected individuals (multipoint LOD = 1.53, *P* = .004, at D14S608) (Cho et al. 1998). Our finding of significant linkage together with the Cedars-Sinai/Parke Davis finding of suggestive linkage to D14S261 satisfies stringent criteria for declaring confirmed linkage to this region of chromosome 14 (Lander and Kruglyak 1995). We propose that the CD-linked locus on chromosome 14q11-12 should be designated the *IBD4* locus. The fact that linkage to this locus has not been detected in three of the five previously published genome scans in IBD is consistent with the expectation that enormous sample sizes are needed for any one study to detect all of the loci that contribute to the genetic susceptibility of a complex trait. In the recent Genetic Analysis Workshop 11, analysis of a simulated data set of a complex trait with four genetic loci, genetic heterogeneity, epistasis, multiple disease alleles at a single locus, and an interacting environmental factor at one of the genetic loci, showed that all of the loci were detected only when all 2,500 nuclear families in the simulated data set were analyzed as one sample (Mandal et al. 1999).

Candidate genes on chromosome 14q11-12 include the T-cell receptor alpha and delta genes (Croce et al. 1985; Chien et al. 1987); interferon-stimulated transcription factor 3, gamma gene (McCusker et al. 1999); a cluster of genes for proteasomes responsible for major histocompatibility complex class I-restricted antigen presentation, including the proteasome subunit, beta-type, 5, proteasome activator subunit 1, and proteasome activator subunit 2 genes (McCusker et al. 1997; Kloetzel et al. 1999); a cluster of hematopoietic serine protease genes, including the cytotoxic T-lymphocyte-associated serine esterase 1, granzyme H, and cathepsin

Table 2

Information Content in Multipoint Analyses (from GENEHUNTER-PLUS Output)

Chromosome	Points[b]	Information Content[a]		
		Average	Max	Min
1	282	.74	.89	.55
2	257	.76	.87	.61
3	217	.75	.89	.56
4	203	.70	.90	.49
5	194	.76	.91	.50
6	181	.72	.85	.59
7	175	.74	.88	.59
8	164	.76	.91	.63
9	155	.76	.87	.58
10	169	.75	.91	.62
11	145	.75	.88	.58
12	165	.76	.91	.59
13	105	.70	.86	.58
14	128	.71	.84	.62
15	117	.76	.88	.61
16	121	.76	.86	.64
17	126	.73	.86	.59
18	127	.75	.88	.57
19	91	.74	.86	.61
20	96	.75	.88	.61
21	55	.73	.85	.53
22	48	.76	.89	.58
X	88	.77	.92	.56

[a] Information content as calculated by GENEHUNTER-PLUS.

[b] Number of locations considered on chromosome (one location every 1 cM).

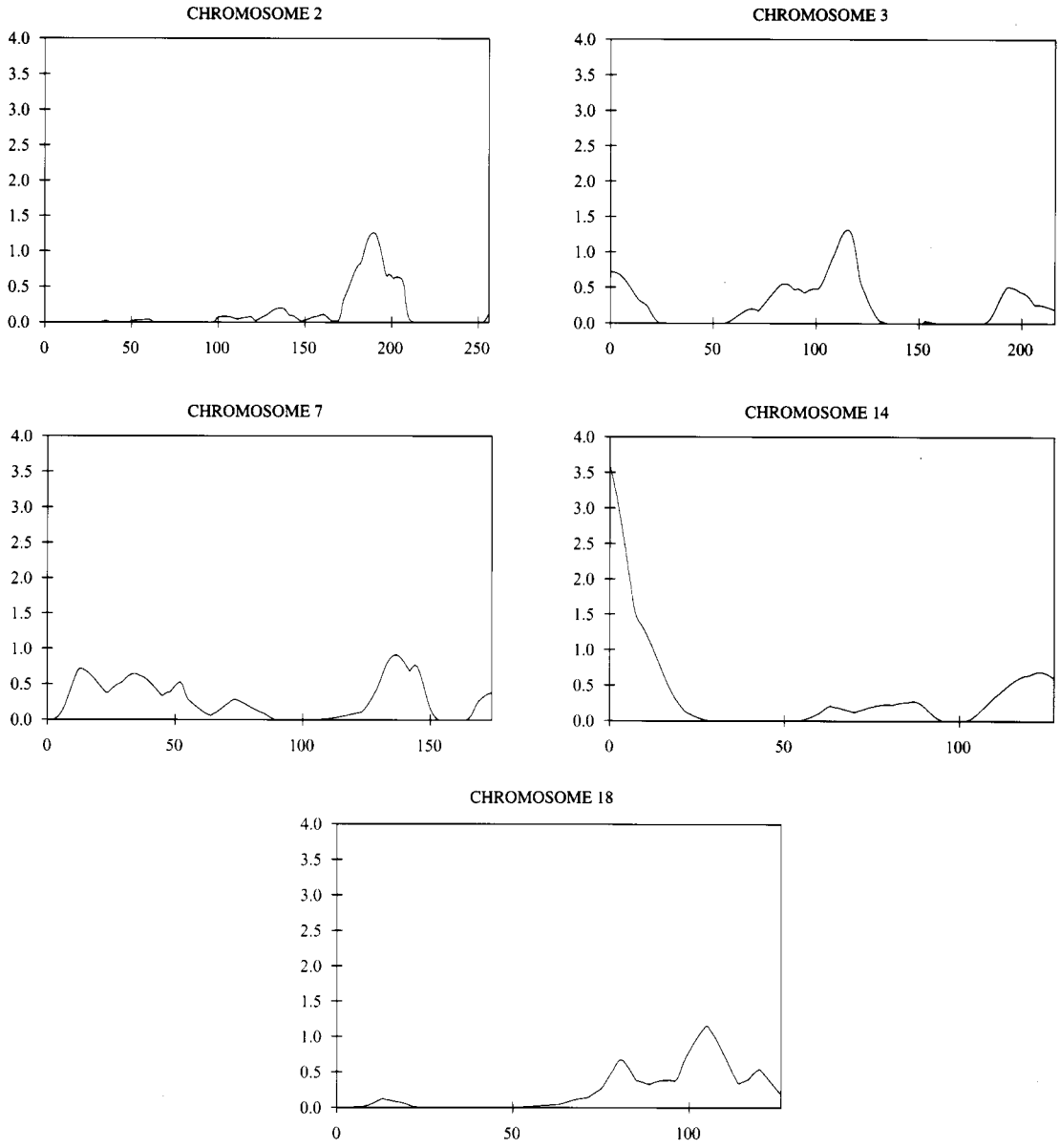

Figure 1 The results of multipoint nonparametric linkage analyses using the S_{pairs} scoring function in the GENEHUNTER-PLUS modification of the GENEHUNTER package (Kruglyak et al. 1996; Kong and Cox 1997) are plotted as the GENEHUNTER-PLUS LOD scores on the Y axis (scale up to LOD = 4) against the genetic distance in centimorgans from the first microsatellite locus on the X axis for chromosomes with multipoint nominal *P* values < .05.

G genes (Hanson et al. 1990); the leukotriene B4 receptor gene (Somers et al. 1997); and the antiapoptotic defender against cell death and BCL2-like 2 genes (Yulug et al. 1995; Gibson et al. 1996).

We did not find evidence for linkage between CD and the *IBD1, IBD2,* or *IBD3* loci (Hugot et al. 1996; Ohmen et al. 1996; Parkes et al. 1996; Satsangi et al. 1996; Akolkar et al. 1998; Brant et al. 1998; Cavanaugh et al. 1998; Cho et al. 1998; Curran et al. 1998; Duerr et al. 1998; Annese et al. 1999; Hampe et al. 1999*a,* 1999*b;* Ma et al. 1999; Silverberg et al. 1999; Yang et al. 1999). Since the multipoint information content in these regions is relatively high in our study (0.79 at D16S753 within the *IBD1* locus, 0.83 at D12S83 within the *IBD2* locus, and 0.84 at D6S2439 within the *IBD3* locus), our lack of replication of linkage is not attributable to low informativeness of the markers that we genotyped in these regions. We assume that we are unable to replicate linkage to *IBD1* and *IBD3* because of locus heterogeneity within CD and lack of sufficient

sample size to replicate the linkage. For a complex trait such as CD, it is expected that a substantially larger data set would be required to replicate a linkage than was required to detect it in the first place (Suarez et al. 1994). Although we and others have previously replicated linkage between IBD and the *IBD2* locus (Satsangi et al. 1996; Akolkar et al. 1998; Curran et al. 1998; Duerr et al. 1998; Hampe et al. 1999*a;* Ma et al. 1999), subsequent data suggests that most of the evidence for linkage to *IBD2* comes from UC families with significantly less linkage evidence in CD families and probable locus heterogeneity within CD at the *IBD2* locus (M. Parkes, M. M. Barmada, J. Satsangi, D. E. Weeks, D. P. Jewell, and R. H. Duerr, unpublished data).

Our finding of nominal evidence for linkage to two adjacent loci on chromosome 18q22 (D18S61 and ATA82B02) is noteworthy, in view of the fact that Ma et al. (1999) also found nominal evidence for linkage between CD and a region centered on D18S474 on chromosome 18q21 (LOD = 1.1 in all families with CD and LOD = 1.9 in Jewish families with CD in the Ma et al. study). While D18S474 is located 33.7 cM centromeric from D18S61 on the Broman et al. genetic map (Broman et al. 1998), we and Ma et al. may have detected the same locus on chromosome 18q, given the limited resolution of allele/haplotype sharing methods of nonparametric linkage analysis for fine localization of disease-susceptibility loci (Boehnke 1994; Kruglyak and Lander 1995, 1996; Roberts et al. 1999).

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Electronic-Database Information

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

Comprehensive Genetic Maps by Broman et al., http://www.marshmed.org/genetics/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CD and *IBD1* [MIM 266600], UC [MIM 191390], *IBD 2* [MIM 601458], and *IBD3* [MIM 604519])

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