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International Collaboration Provides Convincing Linkage Replication in Complex Disease through Analysis of a Large Pooled Data Set: Crohn Disease and Chromosome 16

The IBD International Genetics Consortium*

Numerous familial, non-Mendelian (i.e., complex) diseases have been screened by linkage analysis for regions harboring susceptibility genes. Except for rare, high-penetrance syndromes showing Mendelian inheritance, such as BRCA1 and BRCA2, most attempts have failed to produce replicable linkage findings. For example, in multiple sclerosis and other complex diseases, there have been many reports of significant linkage, followed by numerous failures to replicate. In inflammatory bowel disease (IBD), linkage to two regions has elsewhere been reported at genomewide significance levels: the pericentromeric region on chromosome 16 (IBD1) and chromosome 12q (IBD2). As with other complex diseases, the subsequent support for these localizations has been variable. In this article, we report the results of an international collaborative effort to investigate these putative localization by pooling of data sets that do not individually provide convincing evidence for linkage to these regions. Our results, generated by the genotyping and analysis of 12 microsatellite markers in 613 families, provide unequivocal replication of linkage for a common human disease: a Crohn disease susceptibility locus on chromosome 16 (maximum LOD score 5.79). Despite failure to replicate the previous evidence for linkage on chromosome 12, the results described herein indicate the need to further investigate the potential role of this locus in susceptibility to ulcerative colitis. This report provides a convincing example of the collaborative approach necessary to obtain the sample numbers required to achieve statistical power in studies of complex human traits.

Introduction

The idiopathic inflammatory bowel diseases (IBD)—Crohn disease (CD) and ulcerative colitis (UC)—are common complex genetic disorders with a combined prevalence of ~100–300/100,000 in developed countries. Both diseases involve an excessive inflammatory reaction in the intestines, and symptoms include diarrhea, abdominal pain, and rectal bleeding. Both disorders respond to similar drug therapies. CD can involve any portion of the gastrointestinal tract and all layers of the intestine. The inflammation is patchy and discontinuous, with granulomas observed in some cases. In UC, only the innermost layers of the intestinal wall are involved, although the length of colon involved varies, but the inflammation itself is diffuse and continuous. The early steps in pathogenesis remain undefined in both diseases.

It has been demonstrated that 5%–10% of patients have a first-degree relative who also has IBD (Binder 1998). Among families with more than one affected individual, about 75%–80% are concordant for the same disease within the pedigree and 20% are mixed (having one member with UC and another with CD), with Ashkenazi Jews having both higher disease prevalence and higher familial concordance for both diseases (Binder 1998). Data from twin studies give support to the distinction between the two diseases, with higher concordance rates for monozygotic twins compared to dizygotic twins for the same disorder, but low concordance across disorders. The estimated λ_s is 15–30 for CD and 8–10 for UC (Binder 1998; Yang and Rotter 1999). These data indicate a significant familial component to pathogenesis in these chronic inflammatory disorders.

Before the initiation of the current study, evidence for linkage in two regions had been reported at genomewide significance levels: the pericentromeric region on chromosome 16 (IBD1 [MIM 266600]) (Hugot et al. 1996) and chromosome 12q (IBD2 [MIM 601458]) (Satsangi et al. 1996). Not all follow-up linkage studies, however, replicated these findings (as indicated in tables 1 and 2). Significant differences appeared to exist between these studies, in ethnic mix, numbers of families in each disease type, and genetic markers used. To resolve these differences, we undertook a multicenter linkage study

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Table 1

Evidence for Linkage to IBD1, Indicating Multipoint Linkage Scores, *P* Values, and MAS, for the Peak Location, Recorded for Each Study

Multipoint Score	*P* Value	MAS	No. of Families	Disease (CD/UC/Mixed)	Marker	Reference
3.17[a]	.0004	.64	73	73/0/0	D16S409–D16S419	Hugot et al. (1996)
2.41	.019	.58	79	48/16/15	D16S411	Ohmen et al. (1996)
2.6	.002	…	186	81/64/41	D16S411	Parkes et al. (1996)
2.02	.02	…	70	0/32/38	D16S419	Mirza et al. (1998)
2.49	.007	…	77	77/0/0	D16S769	Brant et al. (1998)
6.3	.0000017	.72	73	54/0/19	D16S409	Cavanaugh et al. (1998)
1.71	.01	.56	274	129/90/50	D16S409–D16S411	Curran et al. (1998); Hampe et al. (1999)
.25	…	…	161	114/36/50	D16S753	Rioux et al. (1998)
2.71	…	…	58	16/23/19	D16S408	Annese et al. (1999)
.69	.5	…	54	47/0/7	D16S411	Vermeire et al. (2000)

[a] The original study identifying the location.

of both regions by examining 613 families with at least two offspring affected with IBD and for which DNA was available from both parents, to critically assess whether the two locations are indeed linked to IBD.

Subjects and Methods

We have studied, from 12 centers on three continents, 613 white nuclear families having two or more sibling pairs with IBD and both parents available for genotyping. Families were chosen only on the basis of completeness and not on prior knowledge of genotyping results. None of these families were included in the original report of linkage on chromosome 16 (Hugot et al. 1996), although 68 families from the United Kingdom were included in the linkage report for chromosome 12 (Satsangi et al. 1996). We specifically excluded these 68 families from analysis of the chromosome 12 data. Families were analyzed as either "pure CD," "pure UC," or, if both diseases occurred in the nuclear family studied, "mixed." Jewish ethnicity was determined by the identification of two or more grandparents as Jewish. Families with both parents affected were excluded. All sites used internationally accepted criteria for diagnosis of IBD, all subjects gave written informed consent, and each institution operated with the approval of the appropriate institutional review board or ethics committee.

Each center genotyped all family members for six markers surrounding each of the proposed localizations for IBD1 on chromosome 16 and IBD2 on chromosome 12. We achieved 98% completion of genotyping. All genotype and family data were anonymized prior to deposition at the data coordinating center, so as to comply with ethical requirements for removal of all identifiers prior to sharing of genotype information. Given the full availability of parental genotypes, allele numbering was assigned sequentially within pedigrees prior to data submission. The inclusion of all parents obviated the need to estimate allele frequencies.

Individuals with records at more than one center were identified by comparing birth date, gender records, and pedigree structure at the central collection site. Individuals thus identified were then compared by initials and were validated by comparison of the first three letters of their first and last names. Raw genotype data for families with duplicate records were compared across centers, and, where discrepancies occurred, genotypes were repeated to obtain consensus or were set to "unknown." Ten North American families with duplicate records were identified and were removed from center-specific records. These families were included only once in the analysis, as a separate North American data set. Results for the 68 English families used in the original description of the IBD2 locus on chromosome 12 were excluded from the analyses for chromosome 12. Results for chromosome 16 markers include all 99 English families.

Nonparametric analyses were performed using Aspex and GENEHUNTER 2.0 (Kruglyak et al. 1996), and results were consistent across statistical programs. Both single-point and multipoint maximum LOD scores (MLSs) were derived at each of the marker loci and for locations between markers. For families with more than two sibs, all possible pairs were formed and included in analysis. No weighting of families with multiple siblings was used; in this case, any downweighting of families with multiple siblings resulted in a higher LOD score, so this choice was conservative. Genotypes that were likely erroneous (as a result of their introducing double-crossovers in short intervals) were removed prior to linkage analysis. After this procedure, the genetic maps derived from the current data were more consistent with published maps.

Heterogeneity tests between N groups were calculated

Table 2

Evidence for Linkage to IBD2, Indicating Multipoint Linkage Scores, *P* Values, and MAS, for the Peak Location, Recorded for Each Study

Maximum Multipoint Score	*P* Value	MAS	No. of Families	Disease (CD/UC/Mixed)	Marker	Reference
5.47[a]	.0000003	.65	160	67/60/33	D12S83	Satsangi et al. (1996)
.6	…	…	77	77/0/0	D12S398	Brant et al. (1998)
1.6	.006	.55	274	134/90/50	D12S379–D12S388	Curran et al. (1998)
.30	.24	…	161	114/36/50	D12S1294	Rioux et al. (1998)
2.76	.00016	…	122	80/22/20	D12S1724–D12S90	Duerr et al. (1998)
2.0	.0004	.62	75	46/16/13	D12S85	Yang et al. (1999)
1.82	.0016	.61	268	129/90/49	D12S303–D12S326	Hampe et al. (1999)
.30	.39	…	54	47/0/7	D12S83	Vermeire et al. (2000)

[a] The original study identifying the location.

as $U = 4.606[\Sigma(\text{MLS1})–\text{MLS2}]$, where Σ(MLS1) is the summed MLS across groups at the given map location and MLS2 is the MLS for all groups pooled. Under the null hypothesis of no heterogeneity, U has a χ^2 distribution with $N - 1$ df.

Results

Twelve groups contributed families from North America, Europe, and Australia. All families were white. Table 3 shows the number of families by center, along with disease, ethnicity (Jewish/non-Jewish), and sibship size. The percentage of families with one affected parent was consistent across sites, at ~10%. For the purpose of comparison, the mean allele sharing (MAS) at all markers on chromosomes 12 and 16 was computed by individual center (table 4) as well as in total.

Multipoint analysis was undertaken on the combined data set and demonstrated strong evidence of linkage to multiple markers on chromosome 16 (table 5). A peak LOD score of 4.96 was seen between markers D16S411 and D16S419 (fig. 1). When the analysis was restricted to the families with CD only, an MLS of 5.79 was observed in the same interval (fig. 1). In contrast, both the pure UC and the mixed families showed no evidence for linkage in this region of chromosome 16. A test of heterogeneity among these three diagnostic groups at the peak multipoint marker (D16S411) is close to significant ($\chi^2 = 5.39$, df = 2, $P = .06$). When the multipoint curves for the three diagnostic groups are examined, it is clear that IBD1 is almost certainly a uniquely CD locus.

A second heterogeneity analysis, designed to examine whether any centers contributed disproportionately to the linkage evidence at IBD1, was performed using the linkage data at the peak marker (D16S411). This test demonstrated that there was no statistical evidence for heterogeneity between centers, either for the whole set of IBD families ($\chi^2 = 10.69$, df = 12, $P > .50$) or for the subset of families with CD only ($\chi^2 = 14.05$, df = 12, $P = .30$). Furthermore, it is clear that the high total MLS is obtained only through combination of results from all centers, since no individual center dominates the linkage evidence (multipoint MLS by center for all IBD is 1.75 [Baltimore] and for CD only is 1.50 [Finland]). Examination of the LOD scores by individual centers reveals no striking linkage evidence, and only the pooled LOD score is remarkable.

Having conclusively confirmed IBD1, we performed

Table 3

Structure of Sample by Site, Indicating the Numbers of Families by Site, Disease, Ethnicity, and Sibship Size

	No. of Families			
	Total	Disease (CD/UC/Mixed)	Ethnicity (Jewish/Non-Jewish)	Sibship Size (2/3/4/5)
Australia	53	36/ 4/ 13	2/ 51	47/ 6/0/0
Belgium	51	40/ 3/ 8	0/ 51	43/ 7/1/0
England:[a]				
Group 1	68	37/ 19/ 12	0/ 99	64/ 4/0/0
Group 2	31	14/ 8/ 9		30/ 1/0/0
Total	99	51/ 27/ 21		94/ 5/0/0
Finland	41	10/ 18/ 13	0/ 41	36/ 4/1/0
France[b]	50	35/ 9/ 6	0/ 50	45/ 4/1/0
Italy	42	13/ 20/ 9	0/ 42	40/ 2/0/0
Baltimore	44	33/ 2/ 9	15/ 29	38/ 5/1/0
Chicago	46	28/ 4/ 14	19/ 27	43/ 2/1/0
Los Angeles	37	37/ 0/ 0	10/ 27	31/ 6/0/0
New York	29	27/ 0/ 2	19/ 10	25/ 4/0/0
Pittsburgh	63	38/ 10/ 15	12/ 51	53/ 8/1/1
Toronto	48	30/ 11/ 7	11/ 37	46/ 2/0/0
North America[c]	10	9/ 0/ 1	4/ 6	8/ 2/0/0
Total	613	386/108/119	92/521	549/57/6/1

[a] Sixty-eight families used in this study (group 1) were used elsewhere to detect IBD2.

[b] None of the families used to detect IBD1 were used in this study.

[c] Families were studied by two or more groups.

Table 4

Results of Two-Point Nonparametric Analyses by Site, Indicating MAS

	Frequency											
Site	D12S85	D12S368	D12S90	D12S83	D12S313	D12S326	D16S403	D16S753	D16S409	D16S411	D16S419	D16S408
Australia (n = 53)	.47	.55	.62	.51	.55	.55	.59	.64	.64	.56	.61	.57
Belgium (n = 51)	.60	.45	.39	.47	.48	.42	.52	.56	.49	.58	.60	.58
England:[a]												
Group 1 (n = 31)	.53	.39	.38	.39	.53	.54						
Total (n= 99)							.52	.53	.52	.53	.49	.54
Finland (n = 41)	.59	.59	.50	.46	.54	.49	.54	.57	.65	.63	.58	.57
France (n = 50)	.49	.54	.51	.49	.50	.49	.63	.58	.56	.60	.65	.60
Italy (n = 42)	.60	.55	.54	.52	.59	.63	.51	.49	.47	.47	.67	.73
Baltimore (n = 44)	.51	.49	.47	.47	.48	.43	.61	.56	.55	.64	.51	.55
Chicago (n = 46)	.48	.54	.45	.52	.52	.52	.48	.54	.52	.51	.51	.50
Los Angeles (n = 37)	.58	.59	.53	.56	.49	.54	.53	.51	.53	.55	.47	.44
New York (n = 29)	.48	.56	.60	.53	.54	.50	.52	.59	.54	.51	.55	.55
Pittsburgh (n = 63)	.63	.55	.54	.57	.50	.50	.52	.52	.53	.53	.58	.56
Toronto (n = 48)	.53	.54	.58	.51	.55	.54	.50	.57	.60	.58	.53	.44
North America[b] (n = 10)	.74	.55	.52	.50	.45	.47	.58	.39	.46	.41	.38	.41
Overall (n = 613)	.55	.53	.51	.50	.52	.51	.54	.55	.55	.55	.56	.55

[a] Sixty-eight families used in the original description of the IBD2 localization were excluded from the analysis of chromosome 12 markers but were included in the analysis of chromosome 16 markers.

[b] Families were studied by two or more groups.

additional analysis to elucidate the action of this locus. We examined, separately, Jewish and non-Jewish families with CD only. There was little difference in allele sharing between these two groups (59% vs. 58% for Jewish vs. non-Jewish, respectively, at D16S409). We also examined allele sharing in two groups of families with CD only: (1) families with a single affected sib pair (ASP), and (2) families with three or more affected sibs (dense families). The excess allele sharing on chromosome 16 was confined to families of group 1 (1 ASP only), with an observed multipoint allele sharing of 60.7% at D16S411 and an MLS of 6.51 (total of 338 ASPs). By contrast, in the denser families of group 2, the allele sharing at the same marker was only 52.8% and the MLS = 0.22 (total of 166 ASPs). The difference in allele sharing between groups 1 and 2 is statistically significant ($\chi 2 = 4.88$, df = 1, $P < .05$).

The level of support for linkage for the IBD2 locus on chromosome 12 is considerably weaker (see table 5). When multipoint analysis was performed, a maximum multipoint LOD score of 1.2 (MAS = .53 at D12S368) was obtained for all disease types combined. The strongest evidence for linkage at IBD2 is in the families with UC, since the largest amount of allele sharing for any marker in this study is seen in families with UC at D12S85 (59%).

Discussion

We have shown that the localization for IBD1 on chromosome 16 is a pure CD locus, and with an MLS of 5.79 in these families, we demonstrate the most compelling statistical evidence to date for a novel genetic localization in complex disease mapping.

The lack of linkage evidence to IBD1 in the dense families with CD is an intriguing finding. This observation may be a consequence of a second rare disease locus segregating in the dense families. Alternatively, we believe that this phenomenon could be a consequence of a high disease-allele frequency on chromosome 16,

Table 5

Multipoint MAS and MLS Results by Disease Type

	Pure CD		Pure UC		Mixed[a]		All IBD	
Marker	MAS	MLS	MAS	MLS	MAS	MLS	MAS	MLS
	n = 349		n = 89		n = 107		n = 545	
D12S85	.53	.5	.59	1.2	.52	.0	.53	1.1
D12S368	.53	.7	.56	.6	.52	.1	.53	1.2
D12S90	.53	.6	.53	.1	.49	.0	.52	.5
D12S83	.53	.7	.49	.0	.48	.0	.52	.3
D12S313	.52	.3	.52	.0	.49	.0	.51	.2
D12S326	.51	.1	.57	.8	.49	.0	.52	.3
	n = 386		n = 108		n = 119		n = 613	
D16S403	.55	1.7	.48	.0	.53	.2	.54	1.4
D16S753	.57	3.8	.51	.0	.52	.1	.55	3.2
D16S409	.58	5.0	.50	.0	.52	.1	.55	3.8
D16S411	.58	5.7	.51	.0	.54	.3	.55	4.9
D16S419	.58	4.8	.50	.0	.53	.2	.56	3.9
D16S408	.57	3.3	.51	.0	.56	.5	.55	3.4

[a] Mixed families are those in which any two first-degree relatives who are affected have different forms of disease.

leading to high levels of disease-allele homozygosity in the population (whether or not such individuals develop disease). Maximizing over models by parametric linkage analyses of these data indicates that the disease-allele frequency may be as high as .35 (data not shown). It is likely that parents who are homozygous for the disease allele would be overrepresented in denser families compared with families having two affected sibs (Rotter 1981). In such families, the ability to detect linkage between the disease and marker locus is reduced, because the disease allele is transmitted with both parental marker alleles. These families will therefore show reduced evidence for linkage. This is not a consequence of loss of information at the marker loci, since, in our data, there is no evidence for excess parental homozygosity in any of the microsatellite markers studied when the dense families are compared to families with two affected siblings (data not shown). These observations concerning the dense families have important implications for study design in complex disease analyses, particularly when disease-allele frequencies are high. In such situations, it would be wise to analyze different types of family structures separately, to detect results such as those reported here.

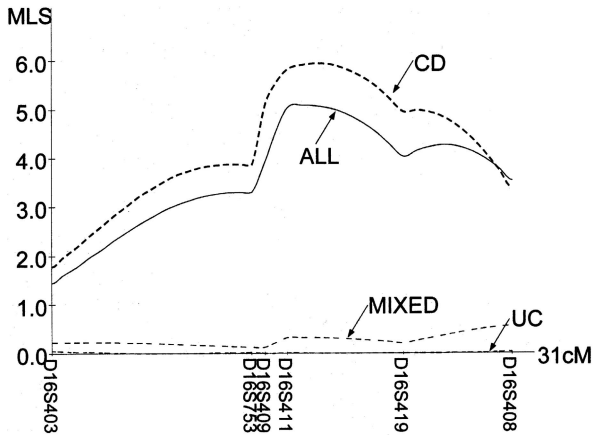

Figure 1 Multipoint LOD score on chromosome 16 by disease group—CD, UC, and mixed—and for all IBD.

On the other hand, the support for linkage to IBD2 is reduced in this sample but is still slightly suggestive, given that this was a replication study. It is possible that this localization is more important for susceptibility to UC than to CD, although far fewer families with UC than with CD were studied. This suggestion has been supported recently by a study by Parkes et al. (2000), using 138 relative pairs affected with UC, in which they showed that IBD2 appears to make a major contribution to susceptibility to UC but to have only a relatively minor effect on susceptibility to CD.

Positional cloning approaches to the identification of disease genes through linkage studies were originally developed for monogenic disorders. Adopting this approach for the identification of susceptibility genes for complex disorders, however, has remained largely unsuccessful. Specifically, such studies have frequently been hampered by failure to replicate linkage findings (Bell and Lathrop 1996; Concannon et al. 1998). Furthermore, most significant results in genetic studies of complex diseases come from the use of the candidate-locus approach (identification of the MHC complex in IDDM susceptibility) rather than from a systematic linkage approach. It is reasonable, however, to expect that many susceptibility genes for complex disorders will probably be loci of modest effect, and, as a consequence, difficulties in localization and nonreplication may result from limitations of power. The results of the present study clearly indicate that, at least in this case, the large number of families necessary for sufficient statistical power could be obtained in the context of a large collaborative effort. This is therefore the first complex human disease for which a truly novel locus, IBD1, identified initially by genomewide linkage studies, has been unequivocally confirmed by a large international collaboration. With these results, studies to identify this gene can now be developed.

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Appendix

The IBD International Genetics Consortium

Members of the consortium are listed according to the contributing center with which they collaborated.

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Electronic-Database Information

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

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

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