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Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity

The Multiple Sclerosis Genetics Group

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Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system. While its etiology is not well understood, genetic factors are clearly involved. Until recently, most genetic studies in MS have been association studies using the case–control design testing specific candidate genes and studying only sporadic cases. The only consistently replicated finding has been an association with the HLA-DR2 allele within the major histocompatibility complex (MHC) on chromosome 6. Using the genetic linkage design, however, evidence for and against linkage of the MHC to MS has been found, fostering suggestions that sporadic and familial MS have different etiologies. Most recently, two of four genomic screens demonstrated linkage to the MHC, although specific allelic associations were not tested. Here, a dataset of 98 multiplex families was studied to test for an association to the HLA-DR2 allele in familial MS and to determine if genetic linkage to the MHC was due solely to such an association. Three highly polymorphic markers (HLA-DR, *D6S273* and TNFβ) in the MHC demonstrated strong genetic linkage (parametric lod scores of 4.60, 2.20 and 1.24, respectively) and a specific association with the HLA-DR2 allele was confirmed (TDT; $P < 0.001$). Stratifying the results by HLA-DR2 status showed that the linkage results were limited to families segregating HLA-DR2 alleles. These results demonstrate that genetic linkage to the MHC can be explained by the HLA-DR2 allelic association. They also indicate that sporadic and familial MS share a common genetic susceptibility. In addition, preliminary calculations suggest that the MHC explains between 17 and 62% of the genetic etiology of MS. This heterogeneity is also supported by the minority of families showing no linkage or association with loci within the MHC.

INTRODUCTION

Multiple sclerosis (MS) is the prototypic human demyelinating disease. In most Caucasian populations, MS is second only to trauma as a cause of acquired neurologic disability arising in early to mid adulthood. MS is an inflammatory disorder believed to result from an autoimmune response directed against central nervous system (CNS) antigens, and myelin proteins in particular, resulting in selective demyelination with relative sparing of axon cylinders, variable loss of oligodendrocytes, and dense astroglio sis (1). The etiology of MS is not well understood. Epidemiologi cal studies support the role of an environmental exposure in MS (2), but to date no virus, viral material, or other agent has been isolated consistently or identified uniquely from MS patients.

Multiple lines of evidence also support the role of genetic factors in susceptibility to MS. First, there are differences in the prevalence of MS among different ethnic groups who reside in the same environment. Individuals of Northern European origin are at highest risk. Second, familial aggregation occurs in MS, resulting in an increased risk to first, second and third degree relatives of probands (3,4). This increase can be anywhere from 15 to 40 times that in the general population. Half sibling studies (5) also suggest that genetic factors are acting in MS. Third, adoption studies (6) have shown an increased risk of MS only in the biological relatives of adopted MS probands. Fourth, twin studies from multiple different populations consistently indicate that a monozygotic twin of an MS patient is at higher risk (25 30% concordance) for MS than is a dizygotic twin (2 5%) (7,8). These data also suggest that a simple Mendelian model of inheritance is unlikely and that susceptibility is largely deter mined by multiple loci, possibly interacting, each with a relatively small contribution to overall risk. Embedded in this complexity may be a small number of major, Mendelian genes that could account for a small proportion of disease, such as has been seen in Alzheimer disease (9) and Parkinson disease (10,11).

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Table 1. C a acte st cs of t e t p ex fa y dataset

T e	No of fa es	No of sa p ed affected d v d a s	No of sa p ed, affected d v d a s	No of sa p ed s -pa s	No of sa p ed affected- e at ve-pa s[a]
T e 1	52	131	281	68	45
T e 2	46	124	197	82	39
Tota	98	255	478	150	84

[a]Av c a a d co s pa s

The genetic region most clearly associated with MS is the major histocompatibility complex (MHC) (12,13). This association has been seen in multiple different populations primarily using datasets of sporadic patients. The majority of studies have focused on Caucasians of Northern European descent, where predisposition to sporadic MS has been associated with the HLA A3, B7, DR2 extended haplotype (14). Using genomic nomenclature, the allelic association is found with the specific DRB1*1501 DQA1*0102 DQB1*0602 haplotype (15). How ever, these studies have used a case control association study design that cannot distinguish between a true genetic effect (either linkage disequilibrium or biological interaction) and a biologi cally irrelevant marker of population admixture. Thus, the positive results with the HLA DR2 allele could arise simply from the migration of Northern European individuals into the other populations. Confirmation of a true genetic effect residing in the MHC would come from a demonstration of linkage disequilib rium through family based tests of allelic association, through positive genetic linkage, or both.

In contrast with the relatively consistent findings in sporadic MS, two published prospective studies of familial MS using sib pairs have not supported linkage to the MHC (16,17). However, several other studies have demonstrated positive lod scores from small sets of families around the world (18 21). In addition, two genomic screens (22,23) have suggested linkage to the MHC. To test for linkage to the MHC and determine if this linkage results from an HLA DR2 association, a larger, prospec tively acquired and rigorously ascertained (24) familial MS dataset was examined.

RESULTS

The dataset of 98 Caucasian families collected from the USA used in these analyses is described in Table 1. These data are divided by tier: the first 52 families were used in the genomic screen, and the remaining 46 families were used as a second independent dataset. These families have a total of 150 genotyped affected sib pairs and 84 genotyped other affected relative pairs. Twenty six (27%) of the families had more than just a single sib pair, 14 (14%) had four or more sampled affected individuals, while eight (8%) had no affected sib pairs at all.

Given the diversity of pedigree structures in our dataset, we performed several different types of linkage analyses to char acterize better the proposed linkage. These analyses included parametric lod scores, affected relative pair analyses, and sib pair analyses. The two point parametric lod scores for HLA DR, *D6S273* and tumor necrosis factor β (TNFβ) are given in Table 2.

The map order used in these analyses is [HLA DR 0.006 *D6S273* 0.004 TNFβ]. Table 2a provides the scores for the autosomal dominant model while Table 2b provides the scores for the autosomal recessive model. All markers provided lod scores >0.00 in each tier, with the strongest overall results arising for the HLA DR locus (Z_{max} = 4.60, Θ = 0.10) using the autosomal dominant model. A parametric multipoint analysis of MS with these markers was attempted using VITESSE (25), but would not run using a Sun Ultra 2 workstation.

The affected relative pair (SimIBD) and two point sib pair results are given in Table 3. While there is a trend toward excess sharing of alleles among affected relatives, only the score for *D6S273* (P = 0.03) reaches nominal significance. As with the parametric lod score, the strongest results arise with the HLA DR locus with a maximum sib pair lod score of 2.60. A multipoint sib pair analysis provided a peak MLS lod score of 2.06 near *D6S273*.

Table 2. Two-po t od sco es t e MHC

Ma ke	T e	0 00	0 05	0 10	0 15	0 20	0 30	0 40
(a) A toso a do		a t two-po t od sco es						
HLA-DR	1	3 14	1 04	1 91	2 05	1 86	1 12	0 38
	2	0 51	2 47	2 70	2 47	2 06	1 09	0 29
	Tota	2 63	3 51	4 60	4 52	3 93	2 21	0 66
D6S273	1	7 26	1 90	0 35	0 33	0 58	0 47	0 14
	2	4 70	0 05	1 20	1 61	1 62	1 11	0 42
	Tota	11 96	1 95	0 86	1 94	2 20	1 58	0 56
TNFβ	1	7 98	2 03	0 35	0 38	0 66	0 58	0 23
	2	7 68	2 58	0 69	0 20	0 57	0 56	0 22
	Tota	15 67	4 61	1 04	0 58	1 24	1 14	0 45
( ) A toso a		ecess ve two-po t od sco es						
HLA-DR	1	2 60	0 39	0 67	1 09	1 15	0 74	0 22
	2	1 74	2 27	2 32	2 12	1 78	0 95	0 26
	Tota	0 86	1 88	2 99	3 21	2 93	1 69	0 48
D6S273	1	5 98	2 96	1 29	0 37	0 10	0 28	0 10
	2	0 89	0 55	1 22	1 44	1 38	0 87	0 28
	Tota	3 11	0 47	0 82	1 36	1 44	0 94	0 28
TNFβ	1	5 79	2 78	1 13	0 23	0 20	0 34	0 13
	2	2 54	0 66	0 31	0 77	0 90	0 64	0 21
	Tota	8 33	3 45	0 82	0 53	1 10	0 98	0 33

Table 3. Ge et c ode -f ee es ts[a]

Ma ke	T e	S IBD *P*-va e	S -pa % s a g	S -pa MLS sco e
HLA-DR	1	0 17	62 9	1 12
	2	0 12	65 7	1 44
	Co ed	0 07	64 3	2 60
D6S273	1	0 20	57 9	0 53
	2	0 03	58 2	0 66
	Co ed	0 03	58 1	1 22
TNFβ	1	0 10	53 7	0 14
	2	0 19	60 1	0 89
	Co ed	0 06	56 8	0 87

[a]A S IBD a a yses we e pe fo ed s g 1000 ep cates to ge e ate t e s ated d st t o

Table 4. L kage es ts sp t y HLA-DR2 stat s

Ma ke	Lod (a toso a do a t)	Lod (a toso a ecess ve)	S IBD *P*-va e	S -pa od sco e
HLA-DR2+ (75 fa es)				
HLA-DR	5 10	4 25	0 12	2 41
D6S273	2 15	1 48	0 05	1 00
TNFβ	1 54	1 06	0 19	0 80
HLA-DR2 (19 fa es)				
HLA-DR	0 00	0 00	0 24	0 00
D6S273	0 01	0 02	0 29	0 06
TNFβ	0 00	0 05	0 22	0 01

To test further the hypothesis that the positive linkage results derived from an allelic association with the HLA DR2 allele, we performed a transmission/disequilibrium test (TDT). Since this dataset was not collected specifically for TDT analysis, it contains a variety of family types and has somewhat limited power to detect an association. Thus two methods of TDT analysis were employed. The most stringent test is the usual TDT using a single affected per family. For this test, we randomly sampled one affected child from each family and collapsed all non HLA DR2 alleles into a single category. A total of 54 possible transmissions of the HLA DR2 allele were observed, with 41 transmitted and 13 not transmitted ($P < 0.001$), thus confirming the HLA DR2/MS association. A more recent extension of the TDT allowing the inclusion of multiple affected sibling data (26) and thus including a different subset of the overall data, provided a *P* value of 0.02 for the HLA DR2 allele, also confirming the association.

To determine if the strong linkage results observed in the overall dataset resulted only from the allelic association of the HLA DR2 allele with MS, the families were divided into two groups based on HLA DR2 status. The first group included families where at least one parental allele was an HLA DR2. The remaining families had no parental HLA DR2 alleles. As expected from the strong association with HLA DR2 observed above, the vast majority of families (75) fell into the HLA DR2+ group. Table 4 presents the linkage results by HLA DR2 status. As the table clearly shows, virtually all the linkage information resides in the HLA DR2+ families.

DISCUSSION

Given the strength and consistency of the HLA DR2 allelic association data in the literature, an association between sporadic MS and HLA DR2 has been generally accepted. However, such an association for familial MS has been more controversial, since past formal genetic linkage studies of the MHC region in MS have yielded quite conflicting results. An initial report by Stewart *et al*. (27) utilized pooled sib pair data from 11 different studies and concluded that a clear MHC effect was present. However, methodological problems with this dataset made interpretation of these findings uncertain. Two prospective studies of the MHC in sib pairs failed to show evidence of linkage. Ebers *et al*. (16) studied 40 affected sib pairs and found random segregation of MHC haplotypes. Although the HLA DR2 allele was increased in frequency in this population, even in HLA DR2+ families biased transmission to affected offspring could not be identified. In a recent report, linkage analysis was performed on 115 sib pairs derived from 109 British families (17). While no increase of HLA haplotype sharing was observed, the HLA DR2 associated haplotype was significantly increased in index siblings and in sporadic MS cases compared with controls. To determine whether linkage was masked by inclusion of families who did not have HLA DR2, families positive for the HLA DR2 haplotype were analyzed separately. No evidence of linkage was found even in this subgroup.

Our results are in direct contrast with the report of Kellar Wood *et al*. (17) and are supported by results seen elsewhere in small sets of families (18,19,21). Not only are there strong linkage results in the current combined sample, the linkage results are restricted to the HLA DR2+ families. There are several possible explanations for this difference. First, a dataset with a larger number of affected collateral relatives was examined with greater power to detect the underlying linkage. Second, diagnostic criteria designed specifically for family studies (28) were used that exclude families in which primary progressive MS is present in the proband. Third, while Kellar Wood *et al*. (17) studied only sib pairs, many larger, multigenerational families where the HLA DR2 effect may be more easily identified were included here. Indeed, the other reported positive linkages (18,19,21) all included at least some large multigenerational families. It is possible that ethnic heterogeneity is one source of conflicting results; however, this seems unlikely as all but one of the current families are Caucasian, and most trace their ancestry to Northern Europe.

The significant allelic association using the TDT approach confirms that a specific association with the HLA DR2 haplotype exists in the current families. This demonstrates the genetic similarity of sporadic and familial MS, and is consistent with earlier limited studies of MHC extended haplotypes in small Caucasian MS families (29,30). Because of the family based nature of the TDT test, significant results will not be observed in the absence of linkage if the association is due to population admixture. Thus, our results further suggest that a biologically meaningful association exists with a locus in this region, a conclusion not possible using the case control design.

Using the elegant formulation of Risch (31), a very rough calculation of the proportion of λ_s that is explained by the HLA DR can be performed. Under the hypothesis of no linkage, 25% of sibships should share no alleles identical by descent (IBD). In our data, only 5% of sibships share no HLA DR alleles IBD. The ratio 0.25/0.05 results in a locus specific λ_s of 5.0. Multiple genetic and epidemiological studies have suggested that the relative risk to siblings (λ_s) of an index MS case is 15 40 times that of the general population. Since the true underlying genetic model is unknown, two simple examples can provide the range of effect that the HLA DR locus may have. At the upper end, under a multiplicative genetic model and assuming a λ_s of 15, the HLA DR association could explain as much as 5/8 (62%) of the genetic etiology of MS. At the lower end, under an additive model and assuming a λ_s of 40, it could explain as little as 5/40 (17%) of the genetic etiology of MS. Even if this lower limit is true, it is important to point out that the strongest results from two whole genome screens (22,23) arose in the MHC, suggesting that this is the strongest (or most prevalent) MS susceptibility locus in man.

Further genetic dissection of the MHC in MS is necessary to determine the susceptibility locus with certainty. The peak parametric lod scores occur at a substantial distance from HLA DR (10 15 cM). However, this distance must be viewed sceptically since it is heavily influenced by parameters we cannot measure, such as locus heterogeneity and incorrect specification of the mode of inheritance. We use parametric lod scores only to examine evidence for linkage, not for specification of the recombination fraction. In fact, the allelic association detected here suggests that the susceptibility allele in the MHC resides on the HLA DR2 extended haplotype. The HLA DR2 allele may itself be the susceptibility allele because of its known affinity to a critical peptide of myelin basic protein (MBP), a possible MS antigen (32,33). However, there are >240 other already identified genes in this region with >30 directly involved in the immune response (1,34), including HLA DR, TNFα, TNFβ, TAP1, TAP2 and MOG. Any one or a combination of these genes could be responsible for the linkage and allelic association seen here. For example, TNFα and TNFβ are closely related cytokines each with a profound role in inflammation and immune regulation (35). Reports of an association of TNF alleles with MS have, in general, indicated that any association is completely explained by the general association with the HLA DR2 extended haplotype (36,37). Another MHC encoded candidate is the transport associated protease (TAP) region (38,39). The potential role of TAP 1 and TAP 2 in several autoimmune diseases including MS has been evaluated, but no association between TAP 1 and TAP 2 polymorphisms independent of the known DR/DQ association has been found (40 43). Myelin oligodendrocyte glycoprotein (MOG), a quantitatively minor but highly encephalitogenic myelin antigen (44), is also located within the MHC. One association study suggested that one restriction fragment length polymorphism (RFLP) of the MOG gene was associated with MS (46), but another association study, employing three microsatellites (two located upstream of the MOG gene and one located in intron 2), concluded that the MOG encoding gene was not associated with MS (45). These additional loci currently are being tested for association within our families.

Restriction of the positive linkage results to the HLA DR2+ families clearly suggests that a number of families (~25% in our sample) have no linkage to the MHC and thus are likely to be influenced by genes in other chromosomal regions. This heterogeneity will strongly influence the results of any linkage or association analyses, making it more difficult to identify these additional genes. We suspect that our multipoint MLS score decreased somewhat from the peak two point MLS score because the HLA DR2 families became more informative (and negative) in the multipoint analysis. This further supports locus heterogeneity in MS. Thus it will be important for future studies to take HLA DR2 status into account when analyzing familial data.

In summary, formal linkage to the MHC has been demonstrated in a population of multiplex MS families and this results from a specific allelic association with HLA DR2. These data strongly indicate that sporadic and familial MS share at least one common genetic susceptibility and that studies of familial MS will help our understanding of sporadic MS as well. In addition, these data support the hypothesis that a genetically determined immune response plays a primary role in the pathogenesis of MS. Furthermore, the MHC locus probably represents less than half of the entire genetic etiology of MS, and quite possibly as little as one sixth of the overall effect. Families not segregating the HLA DR2 allele appear to have no linkage to the MHC and thus must be influenced by other genes. The search for these genes will be crucial in further dissecting the genetic etiology of MS.

MATERIALS AND METHODS

Families

The dataset consists of 98 multiplex families. All families are Caucasian and of Northern or Western European origin and were all collected from the USA. These include the original 52 families used in a genomic screen (23) and an additional 46 families collected using the same criteria. The number of affected sib pairs listed in Table 1 includes only those sib pairs with available DNA. Twenty three of the latter families were also included in the initial follow up dataset (23). Stringent selection criteria, developed collaboratively, have been applied to all family members to ensure that only individuals with 'typical' and clinically well characterized MS are included (24). Virtually all patients in these families have relapsing/remitting disease. Multiplex MS families are located by reference to the MS registry at UCSF, by physician referrals, by collaborative arrangements with other MS centers in the USA, and by advertisements in MS newsletters and at MS functions. The patient's primary physician or designated representative makes initial contact with the propositus in each case; individuals expressing a desire to participate are then contacted by letter. All participants received informed consent as approved by the appropriate IRB. A brief telephone interview is used to help determine eligibility for the study and to collect detailed family history information. At the time of blood drawing, each family member is interviewed and examined by one of the participating neurologists.

Genotyping

White blood cells have been transformed routinely to establish lymphoblastoid cell lines on all family members. Generic HLA DR genotypes were obtained either by serotyping or by PCR using sequence specific primers. Genotypes for the TNFβ and *D6S273* markers were determined using dinucleotide repeat sequence polymorphisms. Primer sequences were obtained from the genome database (GDB: http://gdbwww.gdb.org). Genotypes were determined using standard PCR amplifications,

denaturing gel electrophoresis and silver staining to visualize the results. Details of the silver staining procedure are described elsewhere (47).

Data analysis

All data were entered into the LAPIS data management system and stored in the PEDIGENE® database (48). Data were analyzed for linkage utilizing several different methodologies. Parametric lod score analysis was performed using VITESSE (25). Since the mode of inheritance is not known with certainty, both an autosomal dominant and an autosomal recessive model were used. For both analyses an 'affecteds only' low penetrance analysis (penetrance values of 0.001 for unaffected individuals) was performed, thus eliminating the clinical phenotype informa tion on all individuals not clinically definite for MS. For the autosomal dominant model, a disease allele frequency of 0.05 was assumed, and for the recessive model a disease allele frequency of 0.20 was assumed. A genetic model free analysis using the SimIBD approach (49) was also performed. This allows the inclusion of all affected relatives while not introducing any error due to incorrect model specification. Finally, a specific sib pair analysis on these data was performed. Sib pair analysis is also considered genetic model free (despite actually parameter izing on sib pair sharing), and was performed using the sib phase option of the ASPEX computer package (31,50,51). Family based association studies were done using the TDT (26,52 55). The TDT examines, across families, the transmission of specific alleles from parent to children and can be used as a test of linkage and/or a test of association. Marker allele frequencies were estimated from the families and compared with published frequencies where possible. No significant differences were observed.

Error checking

In order to ensure the greatest accuracy of the data, all attempts were made to fill in every genotype and to minimize errors. To this end, each marker was genotyped to obtain >98% of total possible genotypes. In addition, Mendelian checks of inheritance were performed and extended haplotypes of the three markers were constructed. Haplotypes were examined in two ways. The first was visual inspection of haplotypes. The second was haplotype construction using the SIMWALK program (56). In almost every case, the former approach agreed with the most likely haplotype orientation of the latter. In rare cases, SIM WALK was unable to find a haplotype array with no recombina tion events when such could be identified by visual inspection. Chromosomes with multiple recombination events were geno typed for middle markers. If the events persisted, the remaining markers were regenotyped. Every recombination event ultimate ly was confirmed with multiple genotypes. Through our previous genomic screen, all potential DNA sample and paternity prob lems in the initial 52 families were identified and removed. The second 46 families have been through a similar sample and paternity check.

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