A multigenerational family with multiple sclerosis


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Summary
We report a family with 15 individuals affected with multiple sclerosis present in three and possibly four generations. The segregation of multiple sclerosis within this pedigree is consistent with an autosomal dominant mode of inheritance with reduced penetrance. The clinical characteristics of the affected individuals are indistinguishable from those seen in sporadic multiple sclerosis with respect to sex ratio, age at onset, onset symptom, MRI and clinical course. Eleven of 14 cases (78.6%) were positive for the known multiple sclerosis-associated major histocompatibility complex (MHC) Class II HLA DRB1*15 allele. Parametric linkage analysis gave a non-significant LOD score of 0.31 (θ = 0.33) for the DRB1 gene. However, among 11 affected children with at least one DRB1*15 bearing parent, all 11 out of 11 received at least one copy of this known susceptibility allele. A transmission disequilibrium test analysis was significant for the DRB1*15 allele within this single family; \( P = 0.0054 \). The inheritance pattern in this family suggests the presence of a single major locus responsible for multiple sclerosis susceptibility, with DRB1 acting as an important modifier. This family could be an important resource for the identification of a multiple sclerosis susceptibility gene.

Keywords: multiple sclerosis; familial; MHC; linkage; association

Introduction
There have been many successes in determining the genetic basis of Mendelian disorders, e.g. Duchenne’s muscular dystrophy, Huntington’s disease and cystic fibrosis (Gusella et al., 1983; Kunkel et al., 1985; Rommens et al., 1989). However, it has become apparent from the study of phenotype and genotype correlations that these so-called ‘simple Mendelian’ disorders are more complex than previously thought. For example, phenylketonuria is an autosomal recessive Mendelian trait, but the disease exhibits allelic heterogeneity, modifier loci and environmental factors that all interact to determine the expression of this disease (Scriver and Waters, 1999).

There has been much less success in the genetic dissection of complex diseases. This difficulty has been attributed to underlying complexity encompassing the possibly modest overall contribution of any given gene, the number of genes involved, expected genetic heterogeneity and to higher order interactions among genes and environmental factors. These features, all of which are likely to be operative, represent major obstacles and are most likely responsible for the slowness of progress in identifying disease genes. It has been suggested that the identification of susceptibility loci could require hundreds, if not thousands, of families (Risch and Merikangas, 1996).

In principle, it might be expected that a restricted number of loci could be essential for some diseases. Furthermore, it seems theoretically possible that, in exceptional circumstances, a single genetic abnormality might be sufficiently severe to result in a form of inheritance following a Mendelian pattern. In Alzheimer’s and Parkinson’s diseases, both seemingly complex in their sporadic form, families with Mendelian forms of inheritance have provided considerable insight into disease pathogenesis, in particular regarding the pathways of amyloid deposition in Alzheimer’s disease (St. George-Hyslop et al., 1987; Polymeropoulos et al., 1996).

Despite their possible existence in theory and the strong desire to find them, we are unaware of reports of such families documented among the complex traits believed to be autoimmune in nature (e.g. multiple sclerosis, insulin-dependent diabetes mellitus, rheumatoid arthritis and inflammatory bowel disease). The closest has been those families reported by Bias (1986) in which there was reported a segregation of a variety of autoimmune disorders including multiple sclerosis (Bias et al., 1986), though no genes have
been identified. A possible exception is the lupus-like syndrome observed in hereditary C2 deficiency (Johnson et al., 1992), which is autosomal recessive. In multiple sclerosis, it is rare to find families with more than three or four affected individuals, and pedigrees with more than two consecutive affected generations are rarer still (Ebers et al., 2000). One and two generation nuclear families with many siblings affected with multiple sclerosis are usually too small for meaningful parametric linkage analysis of dominant traits and can represent the chance clustering of multiple, homozygous loci.

We report here an apparently unique family that appears to follow an autosomal dominant segregation pattern with reduced penetrance. If correct, this family has the potential to lead to the identification of a gene with a large effect on pathogenesis and to provide entry into pathways that determine multiple sclerosis susceptibility and insight into the interactions between susceptibility loci, modifiers and the environment.

Material and methods

Ascertainment

The family was ascertained in early 1991 and has been evaluated at regular intervals at family reunions. The family history was recorded and has been regularly updated when required over the last decade (Fig. 1); only a single individual, said to be unaffected, has declined to participate. Otherwise each living affected and unaffected individual has been examined and/or had a history taken by G.C.E. on at least one occasion and, in many cases, three or more times. Medical records were requested and reviewed to confirm historical information and corroborate results. Poser classification was used for multiple sclerosis diagnosis (Poser et al., 1983). A brief synopsis of the clinical aspects of the family is presented here.

DRB1 typing

Genomic DNA was isolated and purified from peripheral blood samples by standard protocols. A polymerase chain reaction (PCR) based method was used to type individuals at the HLA DRB1 locus (Olerup et al., 1992; Ligers et al., 2001). Sequence-specific primers were used to amplify alleles corresponding to HLA DRB1*1, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 alleles and DRB3, DRB4 and DRB5. PCR was performed using the TC-1600 (Intelligent Automation System, Cambridge, MA, USA). PCR conditions were as follows: final volume of 10 μl with 200 ng of genomic DNA, 10 mM Tris–HCl pH 8.3, 50 mM KCl, 1.5 mM MgCl2, 0.60 μmol unlabelled primer, 0.12 μmol [γ-32P]dATP-labelled primer, 200 μM of each dNTP and 0.25 U of Taq DNA polymerase. Cycle conditions were: 94°C for 5 min, 30 cycles of 94°C for 1 min, 61–66°C for 1 min, followed by an elongation step for 5 min at 72°C. Control primers specific for the third intron of the HLA DRB1 gene were also amplified. PCR products were run on 1.5–2% agarose gels, stained with ethidium bromide and visualized with ultraviolet light.

Statistical analysis

An age correction is necessary to estimate risk in Generation IV of this pedigree. Denominator data were adjusted by a weight based upon a previously observed age of onset distribution (Risch, 1983). The Canadian Collaborative Project on the Genetic Susceptibility to Multiple Sclerosis (CCPGSMS) (Sadovnick et al., 1998) was screened for probands having at least two other affected relatives with
clinically confirmed multiple sclerosis. Age of onset data from the 589 multiple sclerosis patients that met the criteria were used to generate the onset distribution curve used for the age correction.

To assess the power to detect linkage in this family, simulations were performed with SLINK of the LINKAGE statistical package (Ott, 1989; Weeks et al., 1990). A hypothetically linked marker with five alleles of equal frequency and a heterozygosity of 0.80 was used. Genotype data for a thousand families were simulated with SLINK and two-point linkage analysis was performed with the MSIM program of The LINKAGE statistical package. The mode of inheritance was assumed to be autosomal dominant and the disease allele frequency was arbitrarily set at 0.001. The penetrance was set at 0.30 in accordance with the observations within this individual family. The phenocopy rate was set at 0.002, approximating the lifetime prevalence of multiple sclerosis in the general population. Linkage analysis was assessed with the same parameters as described for the simulation exercise with the MLINK program of the LINKAGE statistical package (Ott, 1989; Weeks et al., 1990). Transmission disequilibrium analysis was performed by counting the number of times the DRB1*15 of the DRB1 gene was transmitted from heterozygous parents only to affected offspring (Spielman et al., 1993). Whenever possible, parental genotypes were reconstructed based upon the genotypes of unaffected children.

Results

Family overview

The family is referred to as MS-1. The parents of Individuals I-1 and I-2 were both first generation immigrants of German ancestry who emigrated to North America from the northeast region of Germany in the 1870s. The only consanguineous marriages in this pedigree occurred with Individuals II-1 and II-5, who both married their maternal first cousins. Upon repeated questioning, not a single one of the spouses or ‘married-ins’ in Generations II and III had a family history of multiple sclerosis. At the time of initial ascertainment in 1991, there were 12 individuals reported to have multiple sclerosis. During the decade of follow-up, an additional five family members were diagnosed with multiple sclerosis. One individual, thought to have multiple sclerosis at initial ascertainment, was found not to have multiple sclerosis upon neurological examination.

Clinical synopsis of cases at the time of initial ascertainment

Individual I-1

The evidence that this individual may have had multiple sclerosis is historical. He experienced periodic numbness and an inability to walk that required the use of a cane. A son (II-5) stated that his father was progressively unable to support himself and often stumbled when walking in the woods and suffered from a progressive gait disorder. In 1948 at the age of 60 years, Individual I-1 underwent ‘exploratory surgery on his brain’. However, his symptoms with numbness and gait persisted and worsened until his death in 1967. There was no autopsy and a neurological diagnosis was never made. For the purposes of the linkage analysis, this individual has been categorized as unknown.

Individual II-11

This individual was a farmer born in 1924 and who died in 1979. He presented in his mid-20s with weakness of his left lower extremities. A neurologist thought that his progressive symptoms were caused by an intrinsic spinal cord disease. At age 38 years, II-11 experienced an episode of optic neuritis in his right eye. The weakness of his extremities continued to progress and, for the last 5 years of his life, he was a quadriplegic. He died at age 55 years.

Individual II-17

This individual was born in 1937. Her first symptom was remitting numbness in her legs at age 18 years. An MRI was performed in 1989 and showed lesions compatible with multiple sclerosis, at which time she was considered positive for clinically definite multiple sclerosis. She was examined by G.C.E. in a nursing home in 1991 and the diagnosis of multiple sclerosis was confirmed. She died in 1993 at the age of 56 years.

Individual III-1

This individual is currently aged 61 years. He first experienced numbness of his right fourth and fifth fingers extending up the medial aspect of his forearm which subsequently led to neurological investigation at age 49 years. MRI scans were performed on his spinal cord and brain, and both showed lesions compatible with multiple sclerosis at which time he was given the diagnosis of multiple sclerosis. At last contact, this year, he reported no new symptoms and remains fully ambulatory.

Individual III-6

This individual had an inability to detect hot water on one leg at age 18 years. Two years later, she experienced paraesthesia of her right leg lasting ~1 month and, at age 23 years, she experienced numbness of her fingers. Later she developed optic neuritis and Lhermitte’s phenomenon. A recent clinical examination showed bilateral optic atrophy and unilateral Babinski sign: an MRI showed abnormalities compatible with multiple sclerosis.
**Individual III-13**
This individual had a history of a unilateral remitting useless hand syndrome at the age of 21 years. The description was suspicious of a cervical demyelinating plaque. At age 33 years, an MRI showed lesions consistent with multiple sclerosis. For the purposes of the genetic analysis, this individual has been classified as unknown but would satisfy criteria for laboratory-supported possible multiple sclerosis.

**Individual III-15**
This individual had an episode of left optic neuritis at age 30 years. A few months later, she developed remitting numbness of the left side of her body. Four years later, the right side of her body became numb and weak. A neurologist noted decreased sensation to touch on the left side of her face and a left relative afferent pupillary defect. She reported a history of Lhermitte’s phenomenon and an MRI scan at age 34 years showed white matter lesions characteristic of multiple sclerosis.

**Individual III-24**
This individual, at 30 years of age, experienced difficulty in controlling her right hand and tingling sensation in her hand, trunk and chest. She had a mild ataxic and spastic gait when she was 31 years old and a diffuse hyperreflexia with bilateral Babinski sign. At age 33 years, she had an episode of optic neuritis of the right eye and was found to have lesions characteristic of multiple sclerosis upon MRI. She has followed a progressive course over the last decade and has been wheelchair bound for the last 4 years.

**Individual III-32**
This individual had numbness in his upper extremities at the age of 28 years. He followed a relapsing–remitting course for some 5–7 years, but then has been steadily progressing since his mid-30s. A diagnosis of multiple sclerosis was made at age 31 years and was supported by an MRI scan showing typical multiple sclerosis lesions. At the last examination, he showed bilateral internuclear ophthalmoplegia and virtual quadriplegia.

**Individual III-52**
This individual had onset at age 21 years with a tingling sensation in her hands and legs. At age 31 years, she experienced a facial droop and numbness. Subsequently she developed Lhermitte’s phenomenon and has had two episodes of optic neuritis. Over the last several years, she has developed a mild progressive spastic paraparesis but still walks unaided. A recent MRI showed extensive abnormality in the periventricular white matter of both hemispheres characteristic of long standing multiple sclerosis.

**Individual IV-2**
This individual’s initial onset symptom was right hemiparesis that gradually cleared after a few days at age 17 years. A second episode occurred 3 years later with right hand coordination difficulty and a dragging right foot. An MRI showed white matter lesions of both hemispheres and a diagnosis of multiple sclerosis was made. Following a similar exacerbation at age 29 years, there was noted a positive Lhermitte’s phenomenon, a right Babinski sign and a hemiparetic, spastic gait.

**Clinical synopsis of cases identified during prospective follow-up**

**Individual III-28**
This individual was 29 years of age when she had an episode of numbness of her right hand and legs, and an inability to detect temperature in her lower extremities but with preserved touch; this remitted. In 1997, an MRI was performed which displayed a number of small, non-specific lesions in the cerebellar hemispheres compatible with multiple sclerosis. Upon examination this year, a right Babinski sign, mild bilateral finger to nose ataxia and a slight slurring of speech had developed since her first examination. This was in 1993, when she was given the diagnosis of multiple sclerosis.

**Individual III-38**
This individual is a son of II-11 and a brother of III-39. He presented with double vision at age 36 years. An MRI was performed which showed lesions compatible with multiple sclerosis; at that time, a diagnosis of multiple sclerosis was given. In retrospect, he recalls having Lhermitte’s phenomenon and paraesthesiae of his upper left extremity at age 30 years. He was well until the age of 37 years, when he had another attack of double vision with ataxia. The double vision resolved, but he has had persistent problems with balance since that time. A year later, he suffered a case of optic neuritis.

**Individual III-39**
This individual is the brother of III-38 and the son of II-11. Initial onset occurred at age 38 years with numbness and uncoordination of the left hand extending up his forearm without recovery. Abnormal $T_2$ signal focus in the dorsal mid-petalion of the cervical spinal cord at the C3 level of an MRI was consistent with multiple sclerosis. He developed Lhermitte’s phenomenon at age 45 years and continues to have numbness and tingling in his hands and forearm.

**Individual IV-5**
This individual is a daughter of Individual III-28. At age 23 years, she developed numbness in her right arm and hands.
that lasted a month. Lhermitte’s phenomenon developed and was followed by optic neuritis. Abnormal CSF IgG synthesis was found and she was given the diagnosis of multiple sclerosis. Her symptoms were quiescent until age 29 years, when she developed sequential bilateral optic neuritis. A second MRI was performed and showed a plaque consistent with a demyelinating lesion of the upper spinal cord.

**Individual IV-11**
This individual had optic neuritis at age 21 years. Four months later, she experienced optic neuritis in the contralateral eye followed by episodes of painful paraesthesiae in her legs. In 2000, she had a right Babinski sign and an MRI showing lesions characteristic of multiple sclerosis.

**Individuals II-8, III-7 and III-35**
These individuals are parents of multiple sclerosis patients. As potential ‘obligate carriers/transmitters’, they have undergone MRI scans. Individuals III-7 and III-35 showed no evidence of multiple sclerosis lesions on their MRI, while II-8 displayed some periventricular white matter abnormalities which were non-enhancing and would be compatible with a demyelinating process such as multiple sclerosis.

**Clinical summary**
There are 14 cases within this family having a diagnosis of definite or probable multiple sclerosis providing a gender ratio of 1.8 : 1 females to males. Considering that the great-grandfather (I-1) had two children with multiple sclerosis and that he was known to have symptoms suggestive of multiple sclerosis, it is plausible that he had multiple sclerosis and was a carrier for a dominant gene conferring a high risk of multiple sclerosis. If the great-grandfather is counted as affected, the total number of cases is 15 and the female to male ratio is 1.5 : 1. The average age of onset is 27.4 years of age with a range of 17–49 years of age. Among the cases, six patients had a relapsing–remitting form, six patients had a secondary chronic progressive form, one and possibly two patients had a primary progressive form, and one patient had a benign clinical course (see Table 1). One family member, who is categorized as laboratory-supported possible multiple sclerosis, may have a single attack form of multiple sclerosis and, if counted, would increase the number of affected individuals within this family to 16. Additionally, nine individuals had optic neuritis, eight had Lhermitte’s phenomenon and 12 were MRI positive.

**Risk and penetrance estimates**
The penetrance of a hypothetical autosomal dominant multiple sclerosis gene can be estimated from the second and third generations of this pedigree. We will define penetrance as the probability of manifesting multiple sclerosis given the presence of a putative, dominant multiple sclerosis gene.

In Generation II, there were two affected (II-11 and II-17) among 13 siblings for a crude risk of 0.154 (two out of 13). Five unaffected individuals from this generation are assumed to be carriers for the putative gene, as they themselves had children with multiple sclerosis (Fig. 1). Therefore, a total of seven of the 13 children carried the gene (two affected + five unaffected carriers). The penetrance of the hypothetical multiple sclerosis gene can be estimated at two out of seven or 0.286. The other six unaffected siblings had a total of 185 descendants (59 children and 126 grandchildren), none of whom have multiple sclerosis.

In Generation III, there were 57 offspring of the seven gene carriers. The proportion affected is nine out of 57 (0.157). However, several of the cases were offspring of unaffected parents and were themselves the only person affected in their sibship (III-15, III-32 and III-52); the parental carrier status was therefore only determined by having an affected child. An adjustment for ascertainment bias (Davie, 1979) requires the removal of these three cases, making the proportion affected six out of 54 (0.11). Given Mendelian expectations, only half of this generation would have received the gene. The penetrance can be estimated at 0.316 (nine out of 28.5) without the correction and, with the correction for ascertainment, 0.22 (six out of 27). These estimates are relatively close to the 0.286 observed in Generation II.

Generation IV requires certain assumptions in order to estimate risk. The relative age of this generation is young and the 115 individuals are offspring of both carriers and the non-carriers of Generation III. Three people were affected in this generation giving a non-age-adjusted risk of 0.052 (three out of 115/2). Upon age correction, this increases to 0.219 with a 95% confidence interval of 0.047 < P < 0.599 and a penetrance of 0.43. However, the correction for ascertainment bias will decrease this risk substantially from a non-age-adjusted 0.052 to 0.018. The age correction increases this risk estimate to 0.073, with a penetrance of 0.146.

**A decade of follow-up**
There are 370 children, grandchildren and great-grandchildren of I-1 and I-2. There were 354 family members alive and unaffected with multiple sclerosis at the time of initial ascertainment. Even with an annual incidence of six per 100 000 (the highest annual incidence identified in Canada (Paty and Ebers, 1998)), we would expect to see only 0.21 individuals in the family affected with multiple sclerosis over the course of a decade. The observation of five new cases in this cohort of 354 individuals is approximately a 25-fold increase over what is expected in the general population (P = 0.0009). It should also be noted that these five prospectively identified cases occurred in the first degree relatives of family members already identified with multiple sclerosis.
Simulations

The results of a simulation analysis are given in Table 2. If multiple sclerosis is linked to a single gene within this family, we would expect to have enough power to detect linkage given realistic penetrance and marker coverage estimates. The power to obtain a LOD $\geq 1$ was estimated at 97.1%, a LOD $\geq 2$ was 91.6%, and the ability to obtain a LOD $\geq 3$ was 78.9% for this individual family.

**Linkage analysis of DRB1 gene**

A parametric linkage analysis gave a maximum LOD score of 0.31 at a recombination fraction ($\theta$) of 0.33 (Table 3). The mode of inheritance was autosomal dominant, the disease allele frequency was 0.001 and the penetrance was 0.30.

**Transmission disequilibrium test**

There are 11 cases in this family with parents that bear the DRB1*15 allele. In each instance at least one DRB1*15 allele

### Table 1 Summary of clinical findings

<table>
<thead>
<tr>
<th>Person</th>
<th>Sex</th>
<th>Age at onset</th>
<th>Onset symptom</th>
<th>Clinical course</th>
<th>Optic neuritis</th>
<th>Lhermitte’s phenomenon</th>
<th>MRI positive</th>
<th>Multiple sclerosis (Poser et al., 1983)</th>
<th>DRB1 genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI-1</td>
<td>M</td>
<td>Mid-50s</td>
<td>Progressive gait disorder</td>
<td>PPMS?</td>
<td>Unknown</td>
<td>Unknown</td>
<td>N/a</td>
<td>Possible</td>
<td>Unknown</td>
</tr>
<tr>
<td>II-11</td>
<td>M</td>
<td>25</td>
<td>Weakness of left lower extremities</td>
<td>SPMS</td>
<td>Yes</td>
<td>Unknown</td>
<td>N/a</td>
<td>Probable</td>
<td>15,17*</td>
</tr>
<tr>
<td>II-17</td>
<td>F</td>
<td>18</td>
<td>Numbness in legs</td>
<td>SPMS</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Definite</td>
<td>13,15</td>
</tr>
<tr>
<td>III-1</td>
<td>M</td>
<td>49</td>
<td>Right arm numbness</td>
<td>RR</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Definite</td>
<td>11,13</td>
</tr>
<tr>
<td>III-6</td>
<td>F</td>
<td>18</td>
<td>Partial Brown-Sequard syndrome</td>
<td>SPMS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>4,13</td>
</tr>
<tr>
<td>III-13</td>
<td>F</td>
<td>21</td>
<td>Useless right hand syndrome</td>
<td>SAMS</td>
<td>No</td>
<td>No</td>
<td>Equivocal</td>
<td>Laboratory-supported possible</td>
<td>1,15</td>
</tr>
<tr>
<td>III-15</td>
<td>F</td>
<td>30</td>
<td>Left optic neuritis</td>
<td>RR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>4,15</td>
</tr>
<tr>
<td>III-24</td>
<td>F</td>
<td>30</td>
<td>Right hand clumsiness and numbness</td>
<td>SPMS</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Definite</td>
<td>4,15</td>
</tr>
<tr>
<td>III-28</td>
<td>F</td>
<td>29</td>
<td>Right hand and leg numbness</td>
<td>Benign (EDSS &lt;3 at 20 years)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Definite</td>
<td>15,17</td>
</tr>
<tr>
<td>III-32</td>
<td>M</td>
<td>28</td>
<td>Numbness in upper extremities</td>
<td>SPMS</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>4,10</td>
</tr>
<tr>
<td>III-38</td>
<td>M</td>
<td>36</td>
<td>Double vision</td>
<td>RR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>15,15</td>
</tr>
<tr>
<td>III-39</td>
<td>M</td>
<td>38</td>
<td>Left hand numbness</td>
<td>PPMS</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>15,15</td>
</tr>
<tr>
<td>III-52</td>
<td>F</td>
<td>21</td>
<td>Tingling in hands and legs</td>
<td>SPMS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>15,17</td>
</tr>
<tr>
<td>IV-2</td>
<td>F</td>
<td>17</td>
<td>Right hemiparesis</td>
<td>RR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>4,15</td>
</tr>
<tr>
<td>IV-5</td>
<td>F</td>
<td>23</td>
<td>Numbness in right arm</td>
<td>RR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Definite</td>
<td>15,17</td>
</tr>
<tr>
<td>IV-11</td>
<td>F</td>
<td>21</td>
<td>Right optic neuritis</td>
<td>RR</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Definite</td>
<td>15,17</td>
</tr>
</tbody>
</table>

EDSS = Kurtzke Expanded Disability Status Score; N/a = not applicable; RR = relapsing–remitting; SAPMS = single attack primary progressive multiple sclerosis; SPMS = secondary chronic progressive multiple sclerosis. *The genotype of this individual was inferred from the genotype family members.

### Table 2 Results of a simulation analysis

<table>
<thead>
<tr>
<th>Recombination fraction</th>
<th>$\theta = 0.00$</th>
<th>$\theta = 0.05$</th>
<th>$\theta = 0.10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELOD (SD)</td>
<td>4.21 (1.52)</td>
<td>3.89 (1.26)</td>
<td>3.52 (1.26)</td>
</tr>
</tbody>
</table>

Averaged ELOD is the expected LOD score given the simulation parameters.

**Simulations**

The results of a simulation analysis are given in Table 2. If multiple sclerosis is linked to a single gene within this family, we would expect to have enough power to detect linkage given realistic penetrance and marker coverage estimates. The power to obtain a LOD $\geq 1$ was estimated at 97.1%, a LOD $\geq 2$ was 91.6%, and the ability to obtain a LOD $\geq 3$ was 78.9% for this individual family.
was transmitted to the 11 affected offspring. A transmission disequilibrium test (TDT) was then performed (Spielman et al., 1993). There were two parents (II-7 and III-36) who were DRB1*15 positive based upon their children’s genotypes, but who were not genotyped themselves. It could therefore not be determined if they were heterozygous or homozygous for the DRB1*15 allele. As such, they could not be included in the analysis. However, they did transmit their DRB1*15 allele to all three of their affected offspring (III-24, III-28 and IV-11). Also not included in the analysis was Individual III-13, who was the laboratory-supported possible multiple sclerosis case, though she was also DRB1*15 positive. There were eight heterozygous parents, who transmitted the DRB1*15 allele 10 times and did not transmit the DRB1*15 allele once to their affected children (P = 0.0054 by Fisher Exact Test). In the one case where the DRB1*15 allele was not transmitted from one heterozygous parent, the affected offspring received the DRB1*15 allele from the other parent (Individual IV-5).

**Discussion**

The extraordinary claim of a pedigree displaying an autosomal dominant form of a multiple sclerosis-like disorder should engender scepticism and demand extraordinary proof. One family with 12 individuals said to have multiple sclerosis has been previously reported; however, the gender ratio in that family was 10 males to two females and this family had what is now called Pelizaeus–Merzbacher disease (Pelizaeus, 1885). Initially, we doubted the diagnosis of multiple sclerosis and felt the concentration of disease could be an environmental-based cluster. Our experience with many multiplex families has been that pedigrees with large numbers of affected individuals thought to have multiple sclerosis usually have autosomal dominant degenerative conditions such as spinocerebellar ataxias (Paty and Ebers, 1998). We attempted to control for the presence of phenocopies by restricting our first linkage analysis of multiple sclerosis to those patients with optic neuritis, Lhermitte’s phenomenon and internuclear ophthalmoplegia (Ebers et al., 1982). When affected individuals were seen over a decade, it became increasingly clear that the phenotype could not be differentiated from typical multiple sclerosis either by clinical history or neurological examination. Features highly typical of multiple sclerosis such as relapses and remissions, optic neuritis, Lhermitte’s phenomenon and internuclear ophthalmoplegia were all common and mirrored those seen in typical multiple sclerosis. Furthermore, MRI showed lesions of multiple sclerosis either characteristic of or compatible with multiple sclerosis.

In addition to clinical features that led to the diagnosis of multiple sclerosis, there are a number of epidemiological features of the pedigree that further support the diagnosis. Although the numbers are small, the sex ratio is close to that seen in typical multiple sclerosis, i.e. 1.5–2 : 1, females to males. The age of onset for the family MS-1 spans a wide range (17–49 years of age), with the average age being 27 years of age. This is similar to that observed in the general multiple sclerosis population (Weinshenker et al., 1989).

The variable phenotype in such a single family is of some relevance to the question of multiple sclerosis homogeneity and to the interrelationships of the sub-groupings of multiple sclerosis. Among those in the family in which phenotype is sufficiently well characterized, the clinical course spans a broad degree of severity. This includes an individual with a benign form of multiple sclerosis, one individual with a remitting single attack consistent with multiple sclerosis, six individuals with relapsing–remitting disease without progression, one and probably two individuals with primary progressive multiple sclerosis and six individuals with the more typically severe secondary progressive form of the disease (Table 1). These proportions are remarkably close to what is seen in the multiple sclerosis patient population (Paty and Ebers, 1998). If indeed there is a single dominant-acting gene underlying susceptibility within this family, the gene does not seem to determine expressivity of the disease.

The implication that expression may be determined by modifying genes and/or environmental factors is supported by the observations within this family and the observation that MZ concordant twin pairs are strongly concordant for clinical course (G.C. Ebers, unpublished observations).

Additional support for the diagnosis of multiple sclerosis comes from genetic typing; 11 out of 14 (79%) affected family members (where the HLA DRB1 genotypes were determined) were DRB1*15 positive (Table 1) compared with the 30% expected for a group of individuals of northern European ancestry. This is not an expected observation for other hereditary neurodegenerative conditions, but is consistent with multiple sclerosis (Olerup and Hillert, 1991).

The results of parametric linkage analysis did not provide evidence for linkage to the DRB1 gene. This is due to the number of cases that inherited their DRB1*15 gene from a married-in parent and those cases that were DRB1*15 negative. This further demonstrates that HLA is not a linked dominant-acting locus. However, when the transmission of DRB1*15 parental haplotypes was assessed, it became

<table>
<thead>
<tr>
<th>Recombination fraction</th>
<th>0.001</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOD score</td>
<td>−5.1</td>
<td>−2.6</td>
<td>−1.3</td>
<td>−0.10</td>
<td>0.29</td>
<td>0.22</td>
</tr>
</tbody>
</table>

\( Z_{\text{max}} = 0.31 \) at \( \theta = 0.33 \)

**Table 3** Results of linkage analysis to HLA DRB1 gene
apparent that this allele was transmitted uniformly to affected offspring. This implies that the gene is a modifier though not the hypothetical single gene acting to determine multiple sclerosis within this family.

It is clear that dominant inheritance with incomplete penetrance could be invoked for non-Mendelian cases of familial aggregation within a single pedigree and it has often been erroneous. However, in this case there are a number of reasons to propose a pattern. If I-I is considered affected, the trait is present in four successive generations. The penetrance of the disorder is still relatively low in any given sibship, arguing against an unusually high aggregation of susceptibility genes within a single nuclear family. The penetrance appears to be very similar in Generations II, III and IV. The five prospective cases identified prospectively over the last 10 years have all been descendants of the original seven carriers and not of the original five non-carriers of the second generation. Finally, the number of affected individuals suggests that the pedigree is not simply the chance effect of sampling a large number of cases. The next largest family known to us was ascertained by a Canada-wide screen and consists of nine affected individuals (G.C. Ebers, unpublished data).

It may be beneficial for future linkage analyses to perform MRIs on all members of the family in order to ascertain those ‘clinically-silent’ MRI positive individuals—a strategy employed in twin studies (Ebers et al., 1986). We did perform MRIs for three such individuals; the results were negative for two of the family members while the third individual’s MRI was inconclusive. Despite the reduced penetrance, the family presented here should provide sufficient power to detect linkage to an autosomal dominant gene (Table 2). However, given the extreme rarity of this degree of familial aggregation, it is impossible to exclude a variety of potential confounders including the presence of other mechanisms of disease within the pedigree based either upon genetic heterogeneity or phenocopies.

However, it could be hypothesized that a single genetic variant could exert sufficient effect to be the major contributor to risk in a seemingly complex disease in an individual family. Autosomal dominant families that have sufficient power to detect linkage have been demonstrated in Parkinson’s disease, Alzheimer’s disease and breast cancer among others (St. George-Hyslop et al., 1987; Hall et al., 1990; Polymeropoulos et al., 1996). In these diseases, the identification of specific genes, albeit rarely applicable to common forms of disease, has led to the recognition of important disease-related pathways. This pedigree has the potential to illuminate such pathways in a disease where the underlying pathogenesis remains unclear.

Acknowledgements
We wish to thank Doris Buciarelli, Jamie Steckley, Irene Yee and Holly Armstrong for their invaluable assistance to this project and Dr B. Kalman for helpful discussion. We especially wish to thank the members of this family who have been extremely helpful in our research efforts and have shown us tremendous kindness, generosity and support over the last decade. D.A.D. and C.J.W. are supported by Multiple Sclerosis Society of Canada Research Studentship awards.

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A multigenerational family with multiple sclerosis

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