Journal of NeuroVirology (2000) 6, Suppl 2, S10–S14

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The complex genetic aetiology of multiple sclerosis

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A large body of immunologic, epidemiologic, and genetic data indicate that tissue injury in multiple sclerosis (MS) results from an abnormal immune response to one or more myelin antigens that develops in genetically susceptible individuals after exposure to an as-yet undefined casual agent. A genetic component in MS is indicated by an increased relative risk to siblings compared to the general population and an increased concordance rate in monozygotic compared to dizygotic twins. The past few years have seen real progress in defining the genetic basis of MS setting the stage for new approaches for the final characterisation of the genes involved in MS susceptibility and pathogenesis. Whole genome screens conducted in different populations identified discrete chromosomal regions potentially harbouring MS susceptibility genes, however, with the exception of the Major Histocompatibility Complex (MHC) on 6p21, no single locus generated overwhelming evidence of linkage. These results suggest a complex genetic aetiology, including multiple genes of small to moderate effect and probable genetic heterogeneity. The identification and characterisation of MS susceptibility genes and their correlation with disease phenotypes is likely to define the basic aetiology of the disease, improve risk assessment and influence therapeutics. *Journal of NeuroVirology* (2000) **6,** S10–S14.

Keywords: multiple sclerosis; automunity; genetics; major histocompatibility complex

Multiple sclerosis as a genetic disease

Multiple sclerosis (MS) is a common neuro-inflammatory disorder, associated with an autoimmune response directed against myelin proteins within the central nervous system (CNS). The cause of MS remains unknown, although evidence indicates a complex and multifactorial aetiology, with an underlying genetic susceptibility likely acting in concert with undefined environmental exposures. A genetic component in MS pathogenesis is primarily indicated by the increased relative risk to siblings of affected individuals compared with the general population. This familial aggregation (λ_s) can be determined by estimating the ratio of the prevalence in siblings (K_s) *versus* the population prevalence (K) of the disease. For MS, λ_s is between 20 (0.02/0.001) and 40 (0.04/0.001) (Risch 1992). Half-sibling (Sadovnick *et al*, 1996) and adoption (Ebers *et al*, 1995) studies confirm that genetic, and not environmental factors, are responsible for familial aggregation. Twin studies from 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%) (Sadovnick *et al*, 1993; Mumford *et al*, 1994), providing additional evidence for a significant, but complex, genetic aetiology (Table 1). The frequent occurrence of MS in some ethnic populations (particularly those of northern European origin) compared with others (African and Asian groups), irrespective of geographic location also provides evidence for a complex genetic aetiology in MS (Ebers and Sadovnick 1994; Oksenberg *et al*, 1996; Poser, 1995: Compston, 1997). The observation of resistant ethnic groups residing in high risk regions, as for example Gypsies in Bulgaria (Milanov *et al*, 1999), suggests that the relatively low risk in some ethnic groups results primarily from genetic resistance. The genetic component of MS aetiology is believed to result from the action of several susceptibility genes with common alleles (polymorphisms) of weak, but cumulative effects and penetrance. The incomplete penetrance of MS susceptibility alleles probably reflects interactions

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Table 1 Multiple sclerosis as a genetic disease

1. Racial clustering of MS cases. Resistant ethnic groups residing in high risk regions
2. Familial aggregation of MS cases. Increased relative risk to sibs (λ_s=20–40)
3. Low incidence of conjugal MS
4. MS sibling pairs tend to cluster by age of onset, rather than year of onset
5. High disease concordance in monozygotic twins (25–30%) compared with dizygotic twins and non-twin siblings (3–5%)
6. No detectable effect of shared environment on MS susceptibility in first-degree non-biological relatives (spouses, adoptees)
7. Suggestive correlations between certain polymorphic loci and disease susceptibility

Table 2 Confounding factors in genetic studies of multiple sclerosis

1. Aetiologic heterogeneity
   Identical genes, different phenotypes
2. Genetic heterogeneity
   Different genes, identical phenotypes
3. Unknown genetic parameters
   Single *versus* multiple genes
   Dominant *versus* recessive mode of inheritance
   Incomplete penetrance
4. Epistatic gene interactions
5. Post-genomic mechanisms
6. Unidentified non-heritable (environmental) factors

with other genes, post transcriptional regulatory mechanisms, and significant nutritional and environmental influences (Table 2).

The genetic analysis of MS has traditionally focused on association studies of candidate polymorphic genes, in which the frequencies of marker alleles in groups of patients and healthy controls are compared, and the difference is subjected to statistical analysis. Candidate genes are defined as genes that are logical possibilities to play a role in a disease; for MS, candidate genes might encode cytokines, immune-receptors, and proteins involved in viral clearance. The association is often expressed as the relative risk that an individual will develop the disorder if he/she carries the particular allele or marker, compared to an individual who does not carry the allele or marker. With the notable exception of the Major Histocompatibility Complex (MHC or HLA in humans) locus on chromosome 6p21, genetic studies in MS have met with only moderate success in identifying disease-causing or disease-modifying genes (Seboun *et al*, 1996). This is due in part to limitations in study-design (case-control and small sample sizes), the difficulty in selecting from among the many candidate disease gene possibilities, and the modest effect of any single MS susceptibility gene.

The genetic effect of the HLA locus on MS susceptibility has been consistently associated with the class II HLA-DRB1*1501-DQA1*0102-DQB1*0602 haplotype (the molecular designation for the serologically defined 'DR2' haplotype) (Olerup and Hillert, 1991). The mechanism(s) underlying linkage and association of HLA-DRB1*1501-DQA1*0102-DQB1*0602 with MS is not yet fully understood. These MHC molecules may fail to negatively select (delete) autoreactive T cells within the embryonic thymic microenvironment. Alternatively, HLA-DRB1*1501 and/or DQA1*0102-DQB1*0602 genes may encode a class II recognition molecule with a propensity to bind peptide antigens of myelin and stimulate encephalitogenic T cells. Attempts to further localise the MS susceptibility gene within the DR or DQ regions of the MHC have not provided consensus. The strong linkage disequilibrium (LD) across the DR-DQ region has prevented a clear resolution of the relative contribution of each gene.

An alternative strategy to the analysis of candidate genes selected according to their biological function involves first determining the chromosomal region of the genomic defect by genetic linkage analysis, and then isolating the disease gene. This approach for gene localisation requires the collection of pedigrees with more than one affected member and the establishment of linkage by tracking the inheritance of discrete chromosomal segments that co-segregate with the disease. In contrast to monogenic diseases, for complex disorders such as MS, with no evidence of gross chromosomal aberrations, linkage analysis must be performed on an extremely large group of individuals if small genetic effects are to be detected and/or if genetic heterogeneity is present. Genetic heterogeneity means that different genes influence susceptibility to the same phenotype in different individuals. The smaller the genetic contribution, the greater the required sample size, and more stringent the inclusion criteria to minimize effects of clinical heterogeneity. In 1996, three groups completed and reported whole genome screens in

Table 3 Regions of overlap between whole genome scans in multiple scerosis

US	*UK*	*Canada*	*Finland*
	1p36-p33	1p36-p33	
2p23	2p23-p21	2p23-21	
	3p14-p13	3p14-p13	
3q22-q24		3q22-q24	
4q31-qter	4q31-qter		
		5p14-p12	5p14-22
5q13-q23	5q12-q13	5q12-q13	
6p21	6p21		6p21
6q27	6q22-27		
7q11-q22		7q21-q22	
	17q22		17q22-24
18p11		18p11	
19q13	19q12-13	19q13	

familial MS in an attempt to localise genomic regions linked to disease that may include MS susceptibility genes (Ebers *et al*, 1996; MS Genetic Group, 1996; Sawcer *et al*, 1996). A fourth study concentrated on a genetically isolated region of Finland but was based on only 15 families (Kuokkanen *et al*, 1997). The data was analyzed using a combination of parametric (model-based) and non-parametric (model-free) statistical methods. This multi-analytical strategy identified several potential susceptibility regions including the MHC on 6p21 (Table 3). Meta-analysis of all data obtained form genome screening (Lewis *et al*, 1998), comparison of the linkage results to other human and experimental immune-mediated diseases (Becker *et al*, 1998), direct analysis of candidate genes mapped to these regions (MS Genetic Group, 1998), and follow-up screenings in larger datasets of multiplex families (Chataway *et al*, 1998) are currently in progress.

Gene-environment interactions in multiple sclerosis

Epidemiological studies underscore the potential role of non-heritable factors in MS pathogenesis (Kurtzke, 1980). A large number of environmental exposures have been investigated in MS such as viral and bacterial infections, nutritional and dietary factors, well water, exposure to animals, minerals, trauma due to accident or surgery, chemical agents, metals, organic solvents, geographical influences, and other various occupational hazards (Bachmann and Kesselring, 1998; Dalgleish, 1997; Lauer, 1997). Climatic factors such as pollution, solar radiation, temperature, rainfall, humidity, in addition to latitude have all been performed; however, the only consistent independent effect appears to be due to latitude. MS is in general a disease of temperate climates with a population prevalence that decreases with decreasing latitude (Kurtzke, 1980; Kurtzke and Delasnerie-Laupretre, 1996). High incidence rates are found in Scandinavia, Iceland, and the British Isles (about 1 in 1000). Even within the US, distinctions exist in the prevalence of MS between populations living north and south of the 37th parallel (Hogancamp, 1997). The highest reported prevalence of MS, estimated at 250 cases per 100 000 population, occurs in the Orkney Islands north of the mainland of Scotland. MS is uncommon in Japan (2 per 100 000) and other Asian nations, in the sub-Saharan Africa, the Indian sub-continent, and in the native populations of Oceania and the Americas. This characteristic geographical distribution has been used by some investigators to implicate in the aetiology of MS a pathogen that is not ubiquitously distributed. This prevalence pattern can also be explained by the geographical clustering of Northern Europeans with genetic predisposition.

The geographic distribution of MS may alternatively be related to the degree of sunlight exposure catalyzing the production of the hormonally active form of vitamin D:1,25-dihydroxyvitamin D3 or vitamin D3. Exposure to UV light may have a protective effect in MS. In Switzerland for example, MS risk increases at low altitude and decreases at high altitude. In addition to its role in calcium homeostasis and bone metabolism, vitamin D3 possesses both anti-inflammatory and immunomodulatory properties (Issa *et al*, 1998; Cippitelli and Santoni, 1998). Studies of EAE have demonstrated that feeding of vitamin D prevented disease induction and reversed established disease progression (Cantorna *et al*, 1996). Furthermore, vitamin D3 deficiency accelerated EAE onset. Additional evidence is provided by clinical studies which have shown that vitamin D3 deficiency is more prevalent in MS patients, and that MS patients have more frequent fractures and bone loss when compared to age and sex matched controls (Nieves *et al*, 1994; Cosman *et al*, 1998).

Migration studies have also been used to illustrate potential environmental influences on MS (Martyn and Gale, 1997). Children born to parents who have migrated from a high-risk area to a low-risk area for MS appear to have a lower life-time risk than their parents. Conversely, migration of parents from a low-risk area to a high-risk area confers a higher risk for MS in the children. Although the interpretation of migration studies has been difficult, consistent patterns suggest that migration between areas can affect the risk of acquiring MS, and also indicate the existence of a critical age before puberty, between 13–20 years of age, for exposure to the putative environmental agent (Alter *et al*, 1996; Dean *et al*, 1971; Gale and Martyn, 1995). Clusters or outbreaks of MS, such as those described in the Faroe Islands also emphasize the potential role of an infectious agent (Kurtzke *et al*, 1979). Nevertheless, no environmental agent can satisfactorily account for the worldwide distribution of MS and migration patterns of affected individuals.

Various microbes have been implicated in MS pathogenesis. Eighty years ago, spirochetes were claimed to be the cause of MS. This was a reasonable assumption given that syphilis could cause a relapsing/remitting inflammatory disease in the central nervous system with synthesis of oligoclonal immunoglobulins in the cerebrospinal fluid. Since then, more than 20 infectious agents, ranging from retroviruses to mycobacteria have been associated with MS initiation or relapses. Attempts to isolate the causative pathogen have been largely unproductive and failed to provide major insights into mechanisms of disease susceptibility and pathogenesis (Karpuj *et al*, 1997).

Viruses are among the most frequently studied and biologically plausible putative infectious agents related to MS pathogenesis, and many have been proposed to be the causative MS agent. One common approach to investigate viral involvement in MS has been to examine serological titers for specific viruses. Prominent candidates have included measles, rubella, mumps, and the herpesviruses including Epstein Barr virus (EBV), herpes simplex virus (HSV) 1 and 2 and varicella zoster virus (VZV). Higher antibody titers against each of these have been detected in the serum and CSF samples of MS patients when compared to control individuals (Granieri and Casetta, 1997). However, no single virus has proven to have enough specificity and universality to be considered an 'MS pathogen'. The mechanisms that lead to autoimmune destruction of the myelin sheath in MS following infection are unclear. This could occur via nonspecific polyclonal activation of rogue T and B cells by microbial determinants, by molecular mimicry, or by an innocent bystander or superantigen-mediated mechanism (Karpuj *et al*, 1997). If pathogens were involved in disease aetiology, then genetic resistance or susceptibility to a microbial agent would surely have significant consequences for the host. Polymorphisms within chemokine receptors have been shown to significantly influence HIV infection and delay progression to AIDS. Similarly, polymorphisms in cell receptor(s) or other target molecules utilised for viral entry may serve as MS susceptibility genes.

A model of inheritance for multiple sclerosis

A simple model of inheritance for all MS is unlikely and cannot account for the nonlinear decrease in disease risk in families with increasing genetic distance from the MS proband. Taken together, the available data is compatible with a complex multifactorial aetiology in MS, including both genetic and environmental factors. Recurrence risk estimates in first, second, and third degree relatives, combined with twin data, predict that the MS-prone genotype results from multiple independent or interacting genes, each exerting small or moderate effect. Thus MS is most likely a polygenic disorder. It is also possible that genetic heterogeneity exists. Results from our familial MS dataset confirm the genetic importance of the MHC region in conferring susceptibility to MS. Susceptibility may be mediated by the class II genes themselves (DR, DQ or both) related to the known function of these molecules in the normal immune response, e.g. antigen binding and presentation and T cell repertoire determination. The possibility that other genes in the MHC or the telomeric region of the MHC are responsible for the observed genetic effect cannot be excluded. The data also show that although the MHC region plays a significant role in MS susceptibility, much of the genetic effect in MS remains to be explained. By analogy to emerging data on the genetic basis of EAE, it will be of particular interest to identify whether some loci are involved in the initial pathogenic events, while others influence the development and progression of the disease (Schrijver *et al*, 1999; Sciacca *et al*, 1999). Due to the complex heterogeneous nature of MS, large studies of patients using multi-analytical approaches that incorporate gender and reproductive history, genetic polymorphic profiles, as well as detailed clinical, demographic, environmental and serological data, are urgently needed to uncover the pathogenesis of MS and operating genetic risk factors. Their characterization will help to define the basic aetiology of the disease, improve risk assessment and significantly influence the development of novel therapeutic strategies.

Acknowledgments

LF Barcellos is a post-doctoral fellow of the US National Multiple Sclerosis Society.

References

Alter M, Leibowitz U, Speer J (1996). Risk of multiple sclerosis related to age at migration to Israel. *Arch Neurol* **15:** 234–237.

Bachmann S, Kesselring J (1998). Multiple sclerosis and infectious childhood diseases. *Neuroepidemiol* **17:** 154–160.

Becker KG, Simon RM, Bailey-Wilson JE, Freidlin B, Biddison W, McFarland HF, Trent JM (1998). Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases. *Proc Natl Acad Sci USA* **95:** 9979–9984.

Cantorna MT, Hayes CE, DeLuca HF (1996). 1,25-dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *Proc Natl Acad Sci USA* **93:** 7861–7864.

Chataway J, Feakes R, Coraddu F, Gray J, Deans J, Fraser M, Robertson N, Broadley S, Jones H, Clayton D, Goodfellow P, Sawcer S, Compston A (1998). The genetics of multiple sclerosis: principles, background and updated results of the United Kingdom systemic genome screen. *Brain* **121:** 1869–1887.

Cippitelli M, Santoni A (1998). Vitamin D3: a transcriptional modulator of the interferongamma gene. *Eur J Immunol* **28:** 3017–3030.

Compston A (1997). Genetic epidemiology of multiple sclerosis. *J Neurol Neurosurg Psych* **62:** 553–561.

Cosman F, Nieves J, Komar L (1998). Fracture history and bone loss in patients with MS. *Neurol* **51:** 1161–1165.

Dalgleish AG (1997). Viruses and multiple sclerosis. *Acta Neurol Scand* **169** (Suppl): 8–15.

Dean G, Kurtzke JF (1971). On the risk of multiple sclerosis according to age at migration to South Africa. *Br Med J* **3:** 725–729.

Ebers GC, Sadovnick AD, Risch NJ, The Canadian Collaborative Study Group (1995). A genetic basis for familial aggregation in MS. *Nature* **377:** 150–151.

Ebers GC, Sadovnick AD (1994). The role of genetic factors in multiple sclerosis susceptibility. *J Neuroimmunol* **54:** 1–17.

Ebers GC, Kukay K, Bulman DE, Sadovnick AD, Rice G, Anderson C, Armstrong H, Cousin K, Bell RB, Hader W, Paty DW, Hashimoto S, Oger J, Duquette P, Warren S, Gray T, O'Connor P, Nath A, Auty A, Metz L, Francis G, Paulseth JE, Murray TJ, Pryse-Phillips W, Nelson R, Freedman M, Brunet D, Bouchard J-P, Hinds D, Risch N (1996). A full genome search in multiple sclerosis. *Nature Genet* **13:** 472–476.

Gale CR, Martyn CN (1995). Migrant studies in multiple sclerosis. *Prog Neurobiol* **47:** 425–448.

Granieri E, Casetta I (1997). Selected reviews common childhood and adolescent infections and multiple sclerosis. *Neurology* **49:** S42–S54.

Hogancamp WE, Rodriguez M, Weinshenker BG (1997). The epidemology of multiple sclerosis. *Mayo Clin Proc* **72:** 871–878.

Issa LL, Leong GM, Eisman JA (1998). Molecular mechanism of vitamin D receptor action. *Inflamm Res* **47:** 451–475.

Karpuj M, Oksenberg JR, Steinman L (1997). Multiple sclerosis: a polygenic disease involving epistatic interactions, germline rearrangements and environmental effects. *Neurogenet* **1:** 21–28.

Kuokkanen S, Gschwend M, Rioux JD, Daly MJ, Terwilliger JD, Tienari PJ, Wikstrom J, Palo J, Stein LD, Hudson TJ, Lander ES, Peltonen L (1997). Genomewide scan of multiple sclerosis in Finnish multiplex families. *Am J Hum Genet* **61:** 1379–1387.

Kurtzke JF, Hyllested K (1979). Multiple sclerosis in the Faroe Islands: 1. Clinical and epidemiological features. *Ann Neurol* **5:** 6–21.

Kurtzke JF (1980). Epidemiological contribution to multiple sclerosis. An overview. *Neurol* **30** (Suppl 2): 61–79.

Kurtzke JF, Delasnerie-Laupretre N (1996). Reflection on the geographic distribution of multiple sclerosis in France. *Acta Neurol Scand* **93:** 110–117.

Lauer K (1997). Diet and multiple sclerosis. *Neurol* **49** (suppl): 55–61.

Lewis CM, Wise LH, Lanchburry JS (1998). Meta-analysis of genome search results. *Am J Hum Genet* **63:** A1351.

Martyn CN, Gale CR (1997). The epidemiology of multiple sclerosis. *Acta Neurol Scand* **169** (suppl): 3–7.

Milanov I, Topalov N, Kmetski T (1999). Prevalence of multiple sclerosis in Gypsies and Bulgarians. *Epidemiol* **18:** 218–222.

Mumford CJ, Wood NW, Kellar-Wood H, Thorpe J, Miller D, Compston DAS (1994). The British Isles survey of multiple sclerosis in twins. *Neurol* **44:** 11–15.

Nieves J, Cosman F, Herbert J, Shen V, Lindsay R (1994). High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. *Neurol* **44:** 1687–1692.

Oksenberg JR, Seboun E, Hauser SL (1996). Genetics of demyelinating diseases. *Brain Pathol* **6:** 289–302.

Olerup O, Hillert J (1991). HLA class II-associated genetic susceptibility in multiple sclerosis: a critical evaluation. *Tissue Antigens* **38:** 1–15.

Poser CM (1995). Viking voyages: the origin of multiple sclerosis? An essay in medical history. *Acta Neurol Scand* **161** (Suppl): 11–22.

Risch N (1992). Corrections to linkage strategies for genetically complex traits. III. The effect of marker polymorphism on analysis of affected relative pairs. *Am J Hum Genet* **51:** 673–675.

Sadovnick AD, Armstrong H, Rice GPA, Bulman D, Hashimoto L, Paty DW, Hashimoto SA, Warren S, Hader W, Murray TJ (1993). A population-based study of multiple sclerosis in twins: update. *Ann Neurol* **33:** 281–285.

Sadovnick AD, Ebers GC, Dyment DA, Risch NJ and the Canadian Collaborative Study Group (1996). Evidence for genetic basis of multiple sclerosis. *Lancet* **347:** 1728–1730.

Sawcer S, Jones HB, Feakes R, Gray J, Smaldon N, Chataway J, Robertson N, Clayton D, Goodfellow PN, Compston A (1996). A genome screen in multiple sclerosis reveals susceptibility loci on chromosome 6p21 and 17q22. *Nature Genet* **13:** 464–468.

Schrijver HM, Crusius JB, Uitdehaag BM, Garcia Gonzalez MA, Kostense PJ, Polman CH, Pena AS (1999). Association of interleukin-1 beta and interleukin-1 receptor antagonist genes with disease severity in MS. *Neurol* **52:** 595–599.

Sciacca FL, Ferri C, Vandenbroeck K, Vegli F, Gobbi C, Martrinelli F, Franciotta D, Zaffaroni M, Marrosu M, Martinelli V, Comi G, Canal D, Grimaldi LM (1999). Relevance of interleukin 1 receptor antagonist intron 2 polymorphism in Italian MS patients. *Neurol* **10:** 1896–1898.

Seboun E, Oksenberg JR, Hauser SL (1996). Molecular genetics of multiple sclerosis. In: *The molecular and genetic basis of neurological disease*, 2nd edition. Rosenberg RN, Prusiner SB, DiMauro S, Barchi RL, Kunkel LM (eds). Butterworth-Heinemann: Boston, pp 631–662.

The Multiple Sclerosis Genetics Group (1996). A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. *Nature Genet* **13:** 469–471.

The Multiple Sclerosis Genetics Group (1998). Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity. *Hum Molec Genet* **7:** 1229–1234.