Analysis of Multiple Sclerosis as a disease triggered by incompletely penetrant genetic factors

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Summary

Diseases that have a genetic basis are either monogenic (i.e., are controlled by defects at a single locus which are necessary and sufficient to cause disease) or are said to have incompletely penetrant genetic factors (i.e., involve one or more genetic factors that are not individually deterministic of disease). The strong evidence against Multiple Sclerosis being determined by a single gene indicates that multiple genetic and/or environmental factors are required to trigger the disease processes. In addition, there is evidence suggesting that MS is actually a group of diseases with different underlying sets of causes but a similar phenotype. The involvement of multiple factors makes the search for the causes of MS far more complicated than it would be for a monogenic disease.

Hypothesis

MS is an incompletely penetrant genetic disorder that requires two or more factors to be present, either two or more genetic factors, or a combination of genetic and environmental factors.

Experimental tests of the hypothesis

Classifying MS as an incompletely penetrant genetic disorder requires showing that (a) genetic factors do contribute to susceptibility in MS, but that (b) one gene is not sufficient to cause MS by itself.

To address requirement (a), many types of evidence indicate that genetic factors do play a role in causing MS. For instance, numerous familial risk and inheritance studies show an increased risk to family members of people with MS that apparently are not solely due to shared environmental influences. (See our paper “Analysis of inherited genetic susceptibility factors as a possible cause of Multiple Sclerosis.”) In addition, genetic studies of subjects with MS from a variety of geographic regions and ethnicities have identified several possible associations between genes or genomic loci and MS, although most remain tentative with the exception of the HLA region. (See the file *phase2-genetic-studies.xls* for details of each of these studies.)

As for requirement (b), the lack of consistently identifiable Mendelian pedigree patterns in multiplex MS families, the fact that the majority of people with MS report having no

affected family members, and the failure of multiple MS gene searches to single out one overwhelmingly influential gene, collectively indicate that there is no one inherited genetic defect that is solely responsible for all cases of MS. (See "Analysis of Multiple Sclerosis as a Mendelian disease" for more details.) Indeed, most analyses of MS pedigrees support the hypothesis that MS is a multifactorial disease involving multiple genetic and/or environmental components[1-8]. It is theoretically possible that a somatic mutation to a single gene, perhaps operating in conjunction with a particular genetic background, could be responsible for the development of MS. However, there is at present no evidence supporting this hypothesis (see "Analysis of spontaneous genetic mutations as a possible cause of Multiple Sclerosis").

Assuming that MS has a genetic component but is not determined solely by one gene, three possible models exist for the involvement of genetic and non-genetic factors:

(1) MS is a polygenic disease determined by the simultaneous presence of multiple genetic factors
(2) MS risk is also significantly shaped by certain non-genetic or "environmental" factors (infectious agents, toxins, nutritional factors, or trauma)
(3) MS is a group of disorders (some or all with genetic risk factors) that develop via different mechanisms but exhibit similar phenotypes

(1) MS is a polygenic disease determined by the simultaneous presence of multiple genetic factors: Proof that MS falls into this category would be provided by genetic linkage or association studies illuminating an interaction between multiple genes that is necessary and sufficient to cause the disease (as in the recently identified three-locus interaction for Hirschsprung disease[9]). Such an interaction has not yet been identified for MS, although attempts are now being made to find combinations of genes that are associated with MS[10-12].

(2) MS risk is also significantly shaped by non-genetic or environmental factors: The role of environmental factors in triggering MS would be suggested by the association of a particular factor with the development of MS and confirmed by proof that it plays a role in the etiology of the disease. Several environmental factors have been linked with MS in the past – some of recent note include *Chlamydia pneumoniae*, human herpesvirus 6, Epstein-Barr virus, cigarette smoke, vitamin D, and low sunlight exposure. Please refer to the relevant Cure Map documents produced by the Accelerated Cure Project for more information about the evidence produced concerning each of these potential risk factors. At this time, it appears that although several risk factors seem to be viable candidates, no specific environmental factor has yet been conclusively proven to participate in triggering MS.

Despite the absence of confirmed associations and demonstrations of pathological mechanisms for individual environmental risk factors, we can nevertheless examine the epidemiological evidence suggesting that environmental factors *in general* play a role in the development of MS. Demonstrating that MS risk is influenced by environmental factors may be achieved by showing that people with similar genetic characteristics exposed to different environmental factors experience different levels of risk for MS. If genetic factors are constant, then environmental factors are the only variables remaining to explain the risk differential. Two types of analyses that attempt to demonstrate an environmental risk factor through control of the genetic variables are twin studies and migration studies.

Twin concordance evidence: One indication that MS requires one or more environmental factors is the lack of complete concordance between monozygotic (MZ) twins. A disease determined strictly by inherited genetic factors would exhibit 100% concordance in MZ twins, whereas the actual concordance rate seen is 25-30%, suggesting the involvement of environmental triggers. It may be that genetic phenomena such as chance somatic mutations (e.g., in the T cell receptor or immunoglobulin genes) occurring in one twin and not the other could also account for this discrepancy (although one study revealed that healthy twins, like their co-twins with MS, often have skewed T-cell receptor repertoires, suggesting that these somatic changes by themselves may not cause MS[13]). Most sets of identical twins would presumably tend to experience similar environmental exposures, at least during childhood and adolescence, a period suggested as being important for developing susceptibility to MS. However, studies of the discrepancies in environmental exposures (e.g., infections) incurred by discordant twin pairs might eventually provide important insights into non-genetic MS risk factors[14, 15].

Migration risk evidence: Several epidemiological studies have analyzed changes in MS risk for people moving away from their country of origin to a new country associated with a higher or lower risk. These studies have tended, although not with complete consistency, to show a change in risk, possibly correlated with age at time of migration. (See recent studies of immigrants to Jerusalem[16], North African immigrants to France[17], Asian and Caribbean immigrants to England[18], French immigrants to the French West Indies[19], and British and Irish immigrants to Australia[20], as well as a review of 28 prior studies[21].) In addition to a change in prevalence, differences in the phenotype and severity of MS have also been observed in migrant populations[22]. Such findings, if based on proper assumptions and careful control of genetic factors, would provide strong evidence for the importance of environmental risk factors in MS. However, several criticisms have been raised about the methodologies and assumptions used in this studies. For instance:

- Immigrants may not accurately represent the population of their country of origin in terms of age, ethnic origin, health status, etc.
- Comparisons of incidence and prevalence rates from different regions may be problematic. Figures may be influenced by factors such as access to health care, age structure, numbers of doctors per capita (which vary widely around the world), overall awareness of MS, or the ascertainment and diagnostic techniques used. In fact, due to such inconsistencies, even the often-cited latitude gradient of MS risk is now being called into question[23].
- Immigration statistics may not be reliable, leading to an inaccurate calculation of the percentage of immigrants affected.
- Studies typically involve small numbers of subjects and results in some cases may not be statistically significant.

Even studies finding prevalence and incidence discrepancies between different regions within a country (e.g., the northern and southern regions of the US and Australia) have at times been subject to the same types of confounding factors, particularly ethnic origin. For these reasons, migration studies may suggest but cannot be said to have conclusively demonstrated an environmental component to MS risk.

(3) MS is a group of diseases that develop via different mechanisms but exhibit similar phenotypes: One possible explanation for the difficulty of identifying MS genetic susceptibility loci is that MS is not one disease but instead a disorder with numerous subtypes, each caused by a different combination of genetic and/or environmental factors. Such is the case with type 2 diabetes mellitus, a group of metabolic diseases with similar phenotypes but different genetic etiologies (including some monogenic forms) which are often also strongly influenced by environmental factors such as diet and exercise[24]. Support for heterogeneity in MS comes from studies of candidate genes in different groups. For instance, several studies of Japanese MS patients have reported differences in HLA allelic associations between those subjects with "Western-type" MS and those with "Asian-type" MS (the latter of which is characterized by greater opticospinal involvement and may be identical to neuromyelitis optica)[25-31], suggesting that these two related phenotypes have different root causes. At this point it seems reasonable – and certainly more conservative from the standpoint of designing experiments to find MS risk factors – to assume that MS is an etiologically heterogeneous condition rather than a single disease.

Conclusions

Given that current evidence points against MS as a single monogenic disease, the three remaining possibilities are that MS is a polygenic disease, MS is a multifactorial disease involving both genetic and environmental factors, and MS is a group of diseases included in which may be monogenic, polygenic and multifactorial disorders.

At this time, there is no conclusive evidence for or against any of these three possibilities. However, evidence suggesting the involvement of environmental risk factors indicates that experimental and analytical techniques should be developed and used that take their existence into account. It is also quite likely that MS is not a single disease – for instance, the association found for the HLA-DR2 haplotype has not been confirmed in all families nor in all populations, and subtypes of MS have been identified that demonstrate seemingly disparate genetic associations. Therefore, techniques are called for that can either single out causal factors from a combination, or identify subclasses of disease for closer individual study.

References

1 C. Montomoli, I. Prokopenko, A. Caria, R. Ferrai, A. Mander, S. Seaman, L. Musu, M. L. Piras, A. F. Ticca, S. B. Murgia and L. Bernardinelli, *Multiple sclerosis recurrence risk for siblings in an isolated population of Central Sardinia, Italy*. Genet Epidemiol, 2002. **22**(3): p. 265-71. PubMed ID: 11921086.
Study of the recurrence rate in siblings of MS patients in an isolated Sardinian population was estimated as 4.7%. Evidence suggested that the risk to siblings was influenced by the age of onset and possibly the sex of the proband. These results are consistent with a model of a single dominant gene with extremely low penetrance.

2 H. Carton, R. Vlietinck, J. Debruyne, J. De Keyser, M. B. D'Hooghe, R. Loos, R. Medaer, L. Truyen, I. M. Yee and A. D. Sadovnick, *Risks of multiple sclerosis in*

relatives of patients in Flanders, Belgium. J Neurol Neurosurg Psychiatry, 1997. **62**(4): p. 329-33. PubMed ID: 9120443.
Information from 674 Flemish patients and their 26,225 first, second and third degree relatives indicated the risk to parents to be 1.61%, to siblings 2.1%, to children 1.71% and to aunts and uncles 0.66%. These numbers equate to a 10-12x increase in risk for first-degree relatives and a 3x increase for second-degree relatives, and provides support for multilocus contribution to MS susceptibility.

3 D. Lord, A. G. O'Farrell, H. Staunton and E. Keelan, *The inheritance of MS susceptibility*. Ir J Med Sci, 1990. **159 Suppl 8**(p. 1-20. PubMed ID: 2190946.
A variety of oligogenic models was tested against the available population data; the best-fitting simple model for MS was found to be a combination of a recessive gene and dominant X gene with reduced penetrance. The authors estimated the recessive allele to occur in 10-30% of the gene pool, and the X allele to range from 10-72% of the gene pool.

4 M. G. Grasso, M. Frontali, S. Bernardi, P. Pantano and C. Fieschi, *Multifactorial inheritance and recurrence risks of multiple sclerosis in Italian patients*. Neuroepidemiology, 1989. **8**(6): p. 300-7. PubMed ID: 2586700.
An inheritance study based on 166 Italian patients with MS and 332 parents and 326 siblings showed an increase of the disease among relatives that could be best explained by a multifactorial model.

5 D. F. Roberts and D. Bates, *The genetic contribution to multiple sclerosis. Evidence from North- East England*. J Neurol Sci, 1982. **54**(2): p. 287-93. PubMed ID: 7097301.
No evidence of monogenic involvement was found in a study of 206 MS patients and their families from Northeast England. A multifactorial etiology with a polygenic component was viewed as more likely in this cohort.

6 D. F. Roberts, M. J. Roberts and D. C. Poskanzer, *Genetic analysis of multiple sclerosis in Orkney*. J Epidemiol Community Health, 1979. **33**(4): p. 229-35. PubMed ID: 536671.
Familial analysis of all MS patients in Orkney indicated that single locus inheritance is unlikely unless penetrance is very low. Recently introduced genes dominant or codominant in effect were eliminated. Multifactorial involvement was thought to be more likely and the genetic contribution to the etiology of the disease only moderate.

7 A. D. Sadovnick, M. A. Spence and S. Tideman, *A goodness-of-fit test for the polygenic threshold model: application to multiple sclerosis*. Am J Med Genet, 1981. **8**(3): p. 355-61. PubMed ID: 7234906.
Pedigree information from 364 families from British Columbia did not fit a multifactorial model. The authors propose that a major gene could be responsible for at least some of the MS cases in this group.

8 J. W. Lindsey, *Familial recurrence rates and genetic models of multiple sclerosis*. Am J Med Genet A., 2005. **135**(1): p. 53-8. PubMed ID: 15809998.
A computer analysis of MS susceptibility data found that the genetic models that best fit the data featured multiple loci (at least six) with synergistic interaction and autosomal dominant inheritance. The data were also consistent with models with genetic heterogeneity.

9 S. B. Gabriel, R. Salomon, A. Pelet, M. Angrist, J. Amiel, M. Fornage, T. Attie-Bitach, J. M. Olson, R. Hofstra, C. Buys, J. Steffann, A. Munnich, S. Lyonnet and A. Chakravarti, *Segregation at three loci explains familial and population risk in Hirschsprung disease*. Nat Genet, 2002. **31**(1): p. 89-93. PubMed ID: 11953745.
A genome screen of families with the short-segment form of Hirschsprung disease (S-HSCR) identified a trio of susceptibility loci at 3p21, 10q11 and 19q12 that appear to be necessary and sufficient to explain recurrence and incidence data.

10 O. O. Favorova, A. V. Favorov, A. N. Boiko, T. V. Andreewski, M. A. Sudomoina, A. D. Alekseenkov, O. G. Kulakova, E. I. Gusev, G. Parmigiani and M. F. Ochs, *Three allele combinations associated with Multiple Sclerosis*. BMC Med Genet., 2006. **7**(p. 63. PubMed ID: 16872485.
A case-control study of people of Russian descent identified two combinations of three alleles each which perfectly distinguished the MS cases from the controls.

11 D. Brassat, A. A. Motsinger, S. J. Caillier, H. A. Erlich, K. Walker, L. L. Steiner, B. A. Cree, L. F. Barcellos, M. A. Pericak-Vance, S. Schmidt, S. Gregory, S. L. Hauser, J. L. Haines, J. R. Oksenberg and M. D. Ritchie, *Multifactor dimensionality reduction reveals gene-gene interactions associated with multiple sclerosis susceptibility in African Americans*. Genes Immun., 2006. **7**(4): p. 310-5. Epub 2006 Apr 20. PubMed ID: 16625214.
Genotype analysis of an African-American case-control MS data set identified a single-locus and a three-locus association model that predicted MS risk with approximately 75% accuracy.

12 D. A. Dyment, B. M. Herrera, M. Z. Cader, C. J. Willer, M. R. Lincoln, A. D. Sadovnick, N. Risch and G. C. Ebers, *Complex interactions among MHC haplotypes in multiple sclerosis: susceptibility and resistance*. Hum Mol Genet., 2005. **14**(14): p. 2019-26. Epub 2005 Jun 1. PubMed ID: 15930013.
A detailed analysis of genotypes in the HLA region was performed in 4,347 individuals from 873 multiplex MS families. In addition to identifying risk-conferring (DR*15 and DR*17) and protective (DR*14) haplotypes, the analysis also revealed interactions between haplotypes that appear to alter the risk of MS.

13 D. G. Haegert, D. Galutira, T. J. Murray, P. O'Connor and V. Gadag, *Identical twins discordant for multiple sclerosis have a shift in their T-cell receptor repertoires*. Clin Exp Immunol., 2003. **134**(3): p. 532-7. PubMed ID: 14632762.

Analysis of the T-cell receptor distribution in discordant MS twin pairs and in healthy individuals showed that both MS twins affected with MS and their healthy co-twins have shifts in their CDR3 repertoire compared with healthy unrelated individuals. This indicates that CDR3 repertoire shifts precede and enhance the likelihood of developing MS, but do not by themselves cause MS.

14 H. Kuusisto, H. Hyoty, S. Kares, E. Kinnunen, M. Saarelainen and I. Elovaara, *Enteroviruses and the risk of MS in the Finnish Twin Cohort*. Eur J Neurol., 2005. **12**(9): p. 707-9. PubMed ID: 16128872.
No evidence of enterovirus infection was found in serum or CSF taken from twins with MS or from their healthy siblings.

15 G. Ristori, S. Cannoni, M. A. Stazi, N. Vanacore, R. Cotichini, M. Alfo, M. Pugliatti, S. Sotgiu, C. Solaro, R. Bomprezzi, S. Di Giovanni, L. Figa Talamanca, L. Nistico, C. Fagnani, M. C. Neale, I. Cascino, G. Giorgi, M. A. Battaglia, C. Buttinelli, R. Tosi and M. Salvetti, *Multiple sclerosis in twins from continental Italy and Sardinia: a nationwide study*. Ann Neurol., 2006. **59**(1): p. 27-34. PubMed ID: 16240370.
MS twin pairs in continental Italy and Sardinia were identified to calculate twin concordance rates and investigate risk factors for the disease. A few variables, mostly related to infection, were found to influence MS risk and concordance in this cohort.

16 A. Karni, E. Kahana, N. Zilber, O. Abramsky, M. Alter and D. Karussis, *The frequency of multiple sclerosis in jewish and arab populations in greater jerusalem*. Neuroepidemiology, 2003. **22**(1): p. 82-6. PubMed ID: 12566958.
Prevalence rates of MS in the native-born population of greater Jerusalem and in Jewish immigrants to that area were measured. Results suggest that lifestyle differences influencing environmental exposures may affect MS prevalence. Specifically, factors comprising a "Western" lifestyle may increase the risk of MS, and/or factors that are more characteristic of life in Arab countries may protect against MS.

17 J. F. Kurtzke, N. Delasnerie-Laupretre and M. T. Wallin, *Multiple sclerosis in North African migrants to France*. Acta Neurol Scand, 1998. **98**(5): p. 302-9. PubMed ID: 9858098.
A migration study of 260 North African immigrants to France who were diagnosed with MS concludes that MS is an environmental disease acquired after childhood, requires lengthy exposure and incubation periods, and is caused by a widespread infection.

18 G. Dean and M. Elian, *Age at immigration to England of Asian and Caribbean immigrants and the risk of developing multiple sclerosis*. J Neurol Neurosurg Psychiatry, 1997. **63**(5): p. 565-8. PubMed ID: 9408093.
Indian and Pakistani immigrants entering England below the age of 15 incurred a higher risk of developing MS than those who entered the country at a later age. No such differential was observed for Caribbean immigrants.

19 P. Cabre, A. Signate, S. Olindo, H. Merle, D. Caparros-Lefebvre, O. Bera and D. Smadja, *Role of return migration in the emergence of multiple sclerosis in the French West Indies*. Brain., 2005. **128**(Pt 12): p. 2899-910. Epub 2005 Sep 23. PubMed ID: 16183661.
Incidence of MS in Martinique and Guadeloupe was found to be higher in West Indians who had returned to the region after migrating to France. This increase was greater for those who had lived in France before the age of 15. Martinique has a higher rate of return migration and also a higher incidence and prevalence of MS compared with Guadeloupe.

20 S. R. Hammond, D. R. English and J. G. McLeod, *The age-range of risk of developing multiple sclerosis: evidence from a migrant population in Australia*. Brain, 2000. **123**(Pt 5): p. 968-74. PubMed ID: 10775541.
Migrants from the UK and Ireland to Australia experienced a lower prevalence of MS than that of their country of origin except for those who moved to Hobart. The risk for those migrating before age 15 was not significantly different from the risk to those migrating at a later age.

21 C. R. Gale and C. N. Martyn, *Migrant studies in multiple sclerosis*. Prog Neurobiol, 1995. **47**(4-5): p. 425-48. PubMed ID: 8966212.
A review of migration studies in MS points out some of the issues in interpreting their findings, but does note some common patterns with regard to adoption or retention of risk and intergenerational differences in risk.

22 H. Merle, D. Smadja, S. Merle, S. Olindo, A. Signate, A. Donnio, R. Richer, M. Bonnan and P. Cabre, *Visual phenotype of multiple sclerosis in the Afro-Caribbean population and the influence of migration to metropolitan France*. Eur J Ophthalmol., 2005. **15**(3): p. 392-9. PubMed ID: 15945010.
People with MS living in Martinique were identified and classified as to whether they had ever lived in France or had never left the Caribbean basin. Those who had never left were more likely than the migrant group to present with an optical neuropathy and to have more severe visual involvement.

23 R. Zivadinov, L. Iona, L. Monti-Bragadin, A. Bosco, A. Jurjevic, C. Taus, G. Cazzato and M. Zorzon, *The use of standardized incidence and prevalence rates in epidemiological studies on multiple sclerosis. A meta-analysis study*. Neuroepidemiology, 2003. **22**(1): p. 65-74. PubMed ID: 12566956.
A meta-analysis of 127 papers on MS prevalence and 70 papers on MS incidence in various countries found that the latitudinal gradient often reported in MS became less apparent after age and sex adjustment to standard populations was performed.

24 C. P. Busch and R. A. Hegele, *Genetic determinants of type 2 diabetes mellitus*. Clin Genet, 2001. **60**(4): p. 243-54. PubMed ID: 11683767.
Progress in finding genetic determinants of type 2 diabetes is reviewed, including molecular-level insights into several monogenic forms of the disease.

25 J. Kira, T. Kanai, Y. Nishimura, K. Yamasaki, S. Matsushita, Y. Kawano, K. Hasuo, S. Tobimatsu and T. Kobayashi, *Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders*. Ann Neurol, 1996. **40**(4): p. 569-74. PubMed ID: 8871575.
The DRB1*1501 and DRB5*0101 alleles were associated with 34 Japanese patients with Western-type MS but not 23 patients with Asian-type MS. Clinical and imaging differences also suggest that these two types of MS are etiologically different diseases.

26 H. Ito, K. Yamasaki, Y. Kawano, I. Horiuchi, C. Yun, Y. Nishimura and J. Kira, *HLA-DP-associated susceptibility to the optico-spinal form of multiple sclerosis in the Japanese*. Tissue Antigens, 1998. **52**(2): p. 179-82. PubMed ID: 9756407.
The frequencies of DPA1*0202 and DPB1*0501 alleles were found to be significantly increased in 46 patients with Asian-type MS but not 46 patients with Western-type MS.

27 J. J. Ma, M. Nishimura, H. Mine, H. Saji, M. Ohta, K. Saida, K. Ozawa, H. Kawakami, T. Saida and T. Uchiyama, *HLA-DRB1 and tumor necrosis factor gene polymorphisms in Japanese patients with multiple sclerosis*. J Neuroimmunol, 1998. **92**(1-2): p. 109-12. PubMed ID: 9916885.
The association with HLA-DRB1*1501 in Japanese patients with Western-type but not Asian-type MS is confirmed in a study of 42 Western-type and 38 Asian-type patients.

28 T. Ono, M. R. Zambenedetti, K. Yamasaki, Y. Kawano, N. Kamikawaji, H. Ito, M. Sakurai, Y. Nishimura, J. Kira, I. Kanazawa and T. Sasazuki, *Molecular analysis of HLA class I (HLA-A and -B) and HLA class II (HLA- DRB1) genes in Japanese patients with multiple sclerosis (Western type and Asian type)*. Tissue Antigens, 1998. **52**(6): p. 539-42. PubMed ID: 9894852.
The frequency of HLA-DRB1*1501 was increased in 89 Japanese patients with Western-type MS and the frequency of HLA-DRB1*0802 was increased in 57patients with Asian-type MS. HLA-B*5101 was increased in both types of patients compared with controls.

29 K. Yamasaki, I. Horiuchi, M. Minohara, Y. Kawano, Y. Ohyagi, T. Yamada, F. Mihara, H. Ito, Y. Nishimura and J. Kira, *HLA-DPB1*0501-associated opticospinal multiple sclerosis: clinical, neuroimaging and immunogenetic studies*. Brain, 1999. **122**(Pt 9): p. 1689-96. PubMed ID: 10468508.
Clinical and imaging differences, as well as a difference in the frequency of HLA-DPB1*0501, were found between Japanese patients with opticospinal MS and Western-type MS.

30 T. Fukazawa, S. Kikuchi, H. Sasaki, I. Yabe, R. Miyagishi, T. Hamada and K. Tashiro, *Genomic HLA profiles of MS in Hokkaido, Japan: important role of DPB1*0501 allele*. J Neurol, 2000. **247**(3): p. 175-8. PubMed ID: 10787110.
A study of 80 Japanese patients with conventional MS and 17 with opticospinal MS confirmed that DPB1*0501 was associated with OS-MS, but also found it to be higher in conventional MS patients compared with controls.

31 T. Fukazawa, K. Yamasaki, H. Ito, S. Kikuchi, M. Minohara, I. Horiuchi, E. Tsukishima, H. Sasaki, T. Hamada, Y. Nishimura, K. Tashiro and J. Kira, *Both the HLA-CPB1 and -DRB1 alleles correlate with risk for multiple sclerosis in Japanese: clinical phenotypes and gender as important factors*. Tissue Antigens, 2000. **55**(3): p. 199-205. PubMed ID: 10777094.

47 Japanese patients with opticospinal MS were found to have a lower frequency of DPB1*0301 and a higher frequency of DPB1*0501 compared with controls. The 119 patients with conventional MS demonstrated an association with DRB1*1501 and DPB1*0501 (female patients only) and DPB1*0301 (both male and female). No association was found for these HLA alleles with disease course or severity.