



Analysis of inherited genetic susceptibility factors as a possible cause of Multiple Sclerosis

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Summary

Diseases that have an inherited genetic basis are often found to “run in families” due to the transmission of disease genes from one generation to the next. The existence of families with multiple members affected by MS suggests that inherited genes influence the risk of developing MS, at least in some people. Further proof that MS is at least partially heritable comes from studies showing that relatives of people with MS are themselves at increased risk of developing the disease; that this increased risk is greatest for first-degree relatives; and that this risk is not solely due to shared environmental factors. Definitive proof that MS is at least partially heritable will come with the pinpointing of the specific genes that predispose a person to MS.

Hypothesis

Stably inherited genetic factors (as distinguished from spontaneous genetic mutations) either cause MS or influence susceptibility to MS.

Experimental tests of the hypothesis

The types of studies that have been performed to investigate whether susceptibility to MS is influenced by inherited genetic factors include:

1. Documentation of high-risk populations and extended families containing multiple members affected by MS

Initial evidence that a disease has an inherited component may come from observations of extended families containing multiple affected members or populations with elevated prevalence of disease. Various reports of this type can be found in the MS literature¹⁻⁵. Two of these studies even traced the lineage of extended MS families back to the original common ancestors^{3, 5}.

2. Studies of the families of individuals with MS to calculate the percentage of people with MS who have affected family members

Several studies have characterized the familial nature of MS by computing the percentage of MS subjects who have one or more affected family members; this

percentage ranges from less than 10% to 33%, depending on the study and the population characterized⁶⁻¹⁰.

3. Calculations of the incremental MS risk borne by blood relatives of people with MS above the risk seen in the general population

Another way to demonstrate that genes play a role in a given disease is to show that family members of an affected individual are at higher risk than normal of developing the disease themselves.

A special case of this type of study is the twin study. Studies performed of twins in Canada, Finland, France, Denmark, Italy and the British Isles consistently demonstrate that monozygotic twins with a nearly-identical genetic makeup have a higher concordance rate than dizygotic twins who have roughly half of their genes in common¹¹⁻²⁰. Concordance rates varied among the studies, with higher rates reported in geographical regions with relatively high MS prevalence overall and lower rates elsewhere. For example, one study of a high-prevalence region (Canada) found concordance rates of 25.3% in monozygotic (MZ) twins and 5.4% in dizygotic (DZ) twins¹⁷ while in continental Italy the respective rates were 14.5% and 4.0%¹⁹. One study found concordance in approximately 40% of MZ and 10% of DZ twin pairs when subclinical disease activity as indicated by MRI abnormalities typical of MS was included¹⁶.

Other studies have examined the prevalence of MS among parents, children, siblings, aunts, uncles, etc. of people with MS in various populations²¹⁻²⁸. Each of these showed an increased recurrence rate in first-degree relatives, estimated to be as high as 5% for first-degree relatives and even higher in the case of children whose parents both had MS. (General population risk depends on the geographic area studied but is approximately 0.1% in high-risk areas such as northern Europe, the northern U.S. and Canada.) Increased risk to second- and third-degree relatives has also been investigated; for example, one study found the risk for aunts and uncles of people with MS to be 0.66% (the risk to parents, siblings and children was 1.6 to 2.1%)²⁴. An investigation of a Sardinian population found that the recurrence risk was greater in siblings of MS subjects having an onset age less than 30 years and in those having a relative with MS other than a sibling or parent⁵.

In addition to being at higher risk for developing MS, siblings of people with MS were shown by one study to carry an increased risk over population controls of having subclinical characteristics such as CSF-enriched oligoclonal bands, increased CSF IgG antibody titers and elevated serum titers for measles IgG antibody²⁹. An imaging study also found focal white matter lesions in up to 10% of asymptomatic first-degree relatives of people with familial or sporadic MS; however, no evidence of widespread tissue damage was seen in these individuals³⁰.

4. Studies of conjugal, adoptive, and half-sibling relationships to distinguish the effect of inherited genetic factors from environmental factors

Because it is possible that the increased risk to family members could simply be due to common environmental exposures, several studies have sought to separate the genetic and environmental components of MS susceptibility. One study of adoptive families showed that non-biological relatives living with someone with MS were at no higher risk of developing MS than the general population³¹. Another study of half-siblings found no

greater risk for those siblings raised with an affected individual vs. those who were raised apart²³. Finally, studies of spouses and stepsiblings of MS subjects have found their risk to be similar to that of the general population^{26, 32, 33}.

Conclusions

Susceptibility to MS appears to be influenced by inherited genetic factors, at least in the approximately one-fifth of people with MS belonging to families in which multiple cases are found. The existence of multiply affected families and higher prevalence in certain populations/lineages than in others suggests the involvement of either inherited genetic factor(s) and/or common environmental factor(s) affecting people within a close family group.

Support for the involvement of stably inherited genetic susceptibility factors is provided by several observations: (1) an increased risk to relatives which drops off with genetic distance; (2) significantly higher concordance for monozygotic twins (20-30%) than for dizygotic twins or other siblings (approximately 3%); (3) the results of adoption, half-sibling and conjugal studies that rule out environmental factors as the only cause of increased risk in familial MS.

However, inherited genetic factors do not by themselves cause MS. The lack of complete concordance in monozygotic twins indicates that other factors must be involved (such as spontaneous or somatic mutations and/or environmental factors). In addition, 80% of people with MS do not report having an additional affected relative. While there are various ways of explaining this phenomenon, such as a multifactorial disease model requiring certain combinations of inherited and non-inherited factors, it is also possible that some of these “sporadic” cases develop without the involvement of any inherited susceptibility genes.

Family-based linkage and association studies have sought to identify the inherited genetic factors that influence MS risk by searching for genetic loci that segregate with the affected members of families (for example, see Bertrams and Kuwert, 1976³⁴). These studies provide preliminary confirmation that certain genetic susceptibility factor(s) can be transmitted from one generation to the next (see the analyses on susceptibility gene location for more information). Finding a specific gene or genes that can be shown to influence susceptibility to MS and whose MS-associated alleles are stably inherited (versus mutating spontaneously into a pathogenic form) will greatly elucidate the role played by inherited factors in the development of MS. Other research into environmental factors and spontaneous genetic changes will explain why inherited factors do not completely determine MS susceptibility in general.

References

- 1 M. A. Jaworski, J. D. Slater, A. Severini, K. R. Hennig, G. Mansour, J. G. Mehta, R. Jeske, J. Schlaut, C. Y. Pak and J. W. Yoon, *Unusual clustering of diseases in a Canadian Old Colony (Chortitza) Mennonite kindred and community*. Cmaj, 1988. **138**(11): p. 1017-25. PubMed ID: 3370569.

An unusual clustering of suspected autoimmune disease (including MS) was found in a Canadian Old Colony (Chortitza) Mennonite kindred.

- 2 M. A. Jaworski, A. Severini, G. Mansour, K. Hennig, J. D. Slater, R. Jeske, J. Schlaut, J. W. Yoon, N. K. Maclaren and G. T. Nepom, *Inherited diseases in North American Mennonites: focus on Old Colony (Chortitza) Mennonites*. Am J Med Genet, 1989. **32**(2): p. 158-68. PubMed ID: 2784628.

An unusual clustering of suspected autoimmune disease (including MS) was found in a Canadian Old Colony (Chortitza) Mennonite kindred.

- 3 W. J. Hader, T. P. Seland, M. B. Hader, C. J. Harris and D. W. Dietrich, *The occurrence of multiple sclerosis in the Hutterites of North America*. Can J Neurol Sci, 1996. **23**(4): p. 291-5. PubMed ID: 8951208.

Six cases in a Hutterite population of the northwestern US and western Canada were linked to two common ancestors through lines of descent dating to 1723. The authors note that the incidence of MS in Hutterites overall is low, even in this high risk area of North America.

- 4 D. A. Dymont, M. Z. Cader, C. J. Willer, N. Risch, A. D. Sadovnick and G. C. Ebers, *A multigenerational family with multiple sclerosis*. Brain, 2002. **125**(Pt 7): p. 1474-82. PubMed ID: 12076998.

A family was described with 15 affected individuals in three and possibly four generations. The segregation within the pedigree was consistent with an autosomal dominant mode of inheritance with reduced penetrance. 11 out of 14 cases were positive for HLA DRB1*15 allele, and TDT analysis for this allele was significant ($p = 0.0054$). The inheritance pattern suggests a single major locus responsible for MS susceptibility with DRB1 acting as a modifier.

- 5 M. G. Marrosu, M. Lai, E. Cocco, V. Loi, G. Spinicci, M. P. Pischedda, S. Massole, G. Marrosu and P. Contu, *Genetic factors and the founder effect explain familial MS in Sardinia*. Neurology, 2002. **58**(2): p. 283-8. PubMed ID: 11805258.

MS pedigrees and risk factors were studied in 901 Sardinian MS subjects. The recurrence risk was greater in siblings of MS subjects having an onset age less than 30 years and in those having a relative with MS other than a sibling or parent. In one village, all 11 MS subjects descended from 3 pairs of ancestors, with no cases occurring in the remaining 2,346 inhabitants. Prevalence was much higher in descendants from these couples than the regional average and 1.5 times that of the average risk to siblings.

- 6 N. P. Robertson, M. Fraser, J. Deans, D. Clayton, N. Walker and D. A. Compston, *Age-adjusted recurrence risks for relatives of patients with multiple sclerosis*. Brain, 1996. **119**(Pt 2): p. 449-55. PubMed ID: 8800940.

In a study of 674 MS subjects in Cambridgeshire and their relatives, 19% of subjects reported an additionally affected relative. The highest risk was observed for sisters. A systematic reduction in relative risk with the genetic distance from the subject was found, and there was no preferential recurrence for maternal or paternal relatives.

- 7 N. P. Robertson, D. Clayton, M. Fraser, J. Deans and D. A. Compston, *Clinical concordance in sibling pairs with multiple sclerosis*. Neurology, 1996. **47**(2): p. 347-52. PubMed ID: 8757003.

An analysis of clinical, demographic and genetic information on 155 affected sib pairs and 11 trios from the UK found no concordance for age of onset, presenting symptoms or disability at time of assessment. However there was a strong correlation for disease course, a lesser degree of correlation for gender and a minor correlation for year at onset (possibly due to earlier recognition of symptoms in second siblings). The familial recurrence rate was measured at 33%, almost twice a previously reported local rate.

- 8 G. C. Ebers, W. J. Koopman, W. Hader, A. D. Sadovnick, M. Kremenchutzky, P. Mandalfino, D. M. Wingerchuk, J. Baskerville and G. P. Rice, *The natural history of multiple sclerosis: a geographically based study: 8: familial multiple sclerosis*. Brain, 2000. **123 Pt 3**(p. 641-9. PubMed ID: 10686184.

Of a cohort of 1044 MS subjects from Ontario, 19.8% were found to have an affected family member. Comparison of the natural history of familial versus sporadic cases found a high degree of similarity between the two groups, although in the most heavily loaded families, age of onset was lower and the male/female ratio was great.

- 9 V. Sazdovitch, M. H. Verdier-Taillefer, O. Heinzlef, S. Alamowitch and E. Roullet, *[Familial multiple sclerosis: study of 357 consecutive patients]*. Rev Neurol (Paris), 2000. **156**(6-7): p. 638-40. PubMed ID: 10891798.

Based on information from 357 French MS subjects and 4784 of their relatives up to the third degree, 9.8% (35 subjects) had a relative with MS. The familial recurrence rate in France was lower than that found in other countries.

- 10 B. Peterlin, S. Ristiae, J. Sepeiae, B. K. Vracko, A. Rako, L. Lovreeiae, B. Brajenoviae-Miliae, J. Rude, E. Materljan and M. Kapoviae, *Region with persistent high frequency of multiple sclerosis in Croatia and Slovenia*. J Neurol Sci, 2006. **26**(p. 26. PubMed ID: 16806273.

In a high-prevalence region of Croatia and Slovenia (151.9/100,000), 28.7% of the MS subjects ascertained had a history of MS in their first-, second-, or third-degree relatives.

- 11 G. C. Ebers, D. E. Bulman, A. D. Sadovnick, D. W. Paty, S. Warren, W. Hader, T. J. Murray, T. P. Seland, P. Duquette, T. Grey and et al., *A population-based study of multiple sclerosis in twins*. N Engl J Med, 1986. **315**(26): p. 1638-42. PubMed ID: 3785335.

A Canadian twin study of 5463 MS subjects found concordance in seven of 27 monozygotic pairs (25.9%) and one of 43 dizygotic pairs (2.3%). The non-twin sibling concordance rate was 1.9%.

- 12 E. Kinnunen, M. Koskenvuo, J. Kaprio and K. Aho, *Multiple sclerosis in a nationwide series of twins*. *Neurology*, 1987. **37**(10): p. 1627-9. PubMed ID: 3658169.

A review of Finnish Twin Cohort data on 4,063 dizygotic and 9,001 monozygotic same-sexed twin pairs revealed 20 twin pairs (10 monozygotic and 10 dizygotic) in which one twin had MS and one monozygotic pair in which both had MS.

- 13 E. Kinnunen, J. Juntunen, L. Ketonen, S. Koskimies, Y. T. Konttinen, T. Salmi, M. Koskenvuo and J. Kaprio, *Genetic susceptibility to multiple sclerosis. A co-twin study of a nationwide series*. *Arch Neurol*, 1988. **45**(10): p. 1108-11. PubMed ID: 3263109.

Thirteen same-sex Finnish twin pairs in which at least one twin had MS were studied. Two of seven monozygotic twin pairs were concordant for MS; however, none of the six dizygotic pairs were concordant. HLA-DR2 was increased in the subjects studied relative to the general population, but there was no significant segregation of this antigen between MS subjects and their healthy twins.

- 14 *Multiple sclerosis in 54 twinships: concordance rate is independent of zygosity*. French Research Group on Multiple Sclerosis. *Ann Neurol*, 1992. **32**(6): p. 724-7. PubMed ID: 1471862.

A French twin study found the concordance rate for monozygotic twins to be 5.9% (1 out of 17 pairs) and for dizygotic twins to be 2.7% (1 out of 37 pairs). Approximately 30% of clinically unaffected twins had either abnormal MRI results or abnormal visual-evoked potentials. This percentage was independent of zygosity.

- 15 A. D. Sadovnick, H. Armstrong, G. P. Rice, D. Bulman, L. Hashimoto, D. W. Paty, S. A. Hashimoto, S. Warren, W. Hader, T. J. Murray and et al., *A population-based study of multiple sclerosis in twins: update*. *Ann Neurol*, 1993. **33**(3): p. 281-5. PubMed ID: 8498811.

An update to the Canadian twin study after 7.5 years found that the monozygotic concordance rate increased from 25.9 to 30.8% and the dizygotic rate from 2.4 to 4.7%. The twins studied were taken from an overall population of 5,463 MS subjects. The authors conclude that MS susceptibility is influenced by two or more genes as well as environmental factors.

- 16 C. J. Mumford, N. W. Wood, H. Kellar-Wood, J. W. Thorpe, D. H. Miller and D. A. Compston, *The British Isles survey of multiple sclerosis in twins*. *Neurology*, 1994. **44**(1): p. 11-5. PubMed ID: 8290043.

A survey of 105 MS twin pairs in the British Isles found a concordance rate of 25% in monozygotic twins and 3% in dizygotic twins. MRI performed on 64 clinically unaffected twins revealed abnormalities on 13% of the monozygotic twins and 9% of the dizygotic twins.

- 17 C. J. Willer, D. A. Dyment, N. J. Risch, A. D. Sadovnick and G. C. Ebers, *Twin concordance and sibling recurrence rates in multiple sclerosis*. *Proc Natl Acad*

Sci U S A., 2003. **100**(22): p. 12877-82. Epub 2003 Oct 20. PubMed ID: 14569025.

A study of an estimated 75% of all Canadian MS twin pairs produced concordance rates of 25.3% for monozygotic twins, 5.4% for dizygotic twins, and 2.9% for nontwin siblings.

- 18 T. Islam, W. J. Gauderman, W. Cozen, A. S. Hamilton, M. E. Burnett and T. M. Mack, *Differential twin concordance for multiple sclerosis by latitude of birthplace*. Ann Neurol., 2006. **60**(1): p. 56-64. PubMed ID: 16685699.

Concordance for MS among monozygotic twins in a North American study was 2.9 times greater than that determined for dizygotic twins. Concordance was positively associated with latitude.

- 19 G. Ristori, S. Cannoni, M. A. Stazi, N. Vanacore, R. Cotichini, M. Alfo, M. Pugliatti, S. Sotgiu, C. Solaro, R. Bompreszi, 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.

Concordance for MS was 22.2% among monozygotic twins in Sardinia compared with 14.5% for MZ twins in continental Italy. No dizygotic twins concordant for MS were found in Sardinia; the concordance rate for these twins was 4.0% in Continental Italy.

- 20 T. Hansen, A. Skytthe, E. Stenager, H. C. Petersen, H. Bronnum-Hansen and K. O. Kyvik, *Concordance for multiple sclerosis in Danish twins: an update of a nationwide study*. Mult Scler., 2005. **11**(5): p. 504-10. PubMed ID: 16193885.

Among 171 twin pairs identified in a Danish MS registry, 164 were discordant and 7 were concordant. Concordance rates were 24% for monozygotic twins and 3% for dizygotic twins.

- 21 A. D. Sadovnick and P. M. Macleod, *The familial nature of multiple sclerosis: empiric recurrence risks for first, second-, and third-degree relatives of patients*. Neurology, 1981. **31**(8): p. 1039-41. PubMed ID: 7196517.

Relatives of MS subjects, even second- and third-degree relatives, were shown to have a greater risk of developing the disease than the general population, indicating that susceptibility is not entirely due to environmental factors.

- 22 A. D. Sadovnick and P. A. Baird, *The familial nature of multiple sclerosis: age-corrected empiric recurrence risks for children and siblings of patients*. Neurology, 1988. **38**(6): p. 990-1. PubMed ID: 3368082.

Age-adjusted empiric recurrence rates were calculated from data on 815 index cases and over 3,000 siblings and children. The risk of developing MS for these relatives is 3-5%, 30-50 times the rate for the general population.

- 23 A. D. Sadovnick, G. C. Ebers, D. A. Dyment and N. J. Risch, *Evidence for genetic basis of multiple sclerosis. The Canadian Collaborative Study Group*. *Lancet*, 1996. **347**(9017): p. 1728-30. PubMed ID: 8656905.
939 half-sibling sets from a Canadian cohort of 16,000 MS cases were found to have an age-adjusted risk of 1.32% compared with 3.46% for full siblings. No significant difference in risk was found in maternal vs. paternal half-siblings or those raised together compared with those raised apart. The authors concluded that shared environmental factors and maternal effects (intrauterine and perinatal factors, breastfeeding and genomic imprinting) have no demonstrable effect on familial risk.
- 24 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 MS subjects 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.
- 25 N. P. Robertson, J. I. O'Riordan, J. Chataway, D. P. Kingsley, D. H. Miller, D. Clayton and D. A. Compston, *Offspring recurrence rates and clinical characteristics of conjugal multiple sclerosis*. *Lancet*, 1997. **349**(9065): p. 1587-90. PubMed ID: 9174560.
Five of the 86 children (6%) of 45 affected conjugal pairs had clinically definite MS; a further five had either imaging abnormalities or clinical symptoms, but not clinically definite MS. In those spouses who were symptom-free before they met, no evidence was seen of clinical concordance, clustering at year of onset, or distortion of expected age of onset in the second affected spouse.
- 26 G. C. Ebers, I. M. Yee, A. D. Sadovnick and P. Duquette, *Conjugal multiple sclerosis: population-based prevalence and recurrence risks in offspring. Canadian Collaborative Study Group*. *Ann Neurol*, 2000. **48**(6): p. 927-31. PubMed ID: 11117550.
A study of the frequency of conjugal MS found the risk of MS in spouses to be 0.17% (23 cases among 13,550 spouses of study probands), similar to the risk for the general population. Six of the 49 offspring of conjugal pairs had MS, giving an age-adjusted rate similar to the concordance rate for monozygotic twins. The low risk for spouses and the high risk for offspring support the hypothesis that familial risk is genetically determined.
- 27 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 subjects 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.

- 28 I. Prokopenko, C. Montomoli, R. Ferrai, L. Musu, M. L. Piras, A. Ticca, B. S. Murgia and L. Bernardinelli, *Risk for relatives of patients with multiple sclerosis in central Sardinia, Italy*. Neuroepidemiology., 2003. **22**(5): p. 290-6. PubMed ID: 12902624.

Recurrence rates were calculated for MS subjects in central Sardinia as 1.26% (parents), 2.33% (children), 4.76% (siblings), 0.72% (second-degree relatives), and 1.79% (third-degree relatives).

- 29 S. Haghghi, O. Andersen, L. Rosengren, T. Bergstrom, J. Wahlstrom and S. Nilsson, *Incidence of CSF abnormalities in siblings of multiple sclerosis patients and unrelated controls*. J Neurol, 2000. **247**(8): p. 616-22. PubMed ID: 11041329.

Healthy siblings of MS subjects were more likely than unrelated controls to have CSF-enriched oligoclonal bands; siblings also had increased CSF IgG antibody titers and serum titers for measles IgG antibody than unrelated controls. The rate for this partially hyperimmune condition was approximately five times the rate for clinically definite MS in siblings. These findings suggest that a genetic trait interacts with infections to cause MS.

- 30 N. De Stefano, E. Cocco, M. Lai, M. Battaglini, A. Spissu, P. Marchi, G. Floris, M. Mortilla, M. L. Stromillo, A. Paolillo, A. Federico and M. G. Marrosu, *Imaging brain damage in first-degree relatives of sporadic and familial multiple sclerosis*. Ann Neurol., 2006. **59**(4): p. 634-9. PubMed ID: 16498621.

Brain MRI and magnetization transfer (MT) imaging was performed on 240 first-degree relatives of people with MS. Lesions similar to those seen in MS were found in 4% of relatives of subjects with sporadic MS and 10% of subjects with familial MS. However, no normal appearing white matter abnormalities or brain atrophy was found in the relatives compared with normal controls.

- 31 G. C. Ebers, A. D. Sadovnick and N. J. Risch, *A genetic basis for familial aggregation in multiple sclerosis*. Canadian Collaborative Study Group. Nature, 1995. **377**(6545): p. 150-1. PubMed ID: 7675080.

A questionnaire administered to 15,000 individuals with MS to find adoption situations revealed the risk to first-degree non-biological relatives living with the index case was no greater than that of the general population. This indicates that familial aggregation is due to genetic factors as opposed to sharing of the same environment.

- 32 D. A. Dyment, I. M. Yee, G. C. Ebers and A. D. Sadovnick, *Multiple sclerosis in stepsiblings: recurrence risk and ascertainment*. J Neurol Neurosurg Psychiatry., 2006. **77**(2): p. 258-9. PubMed ID: 16421134.

No increased risk of MS above that found in the general population was determined for step-siblings of people with MS.

- 33 N. M. Nielsen, T. Westergaard, K. Rostgaard, M. Frisch, H. Hjalgrim, J. Wohlfahrt, N. Koch-Henriksen and M. Melbye, *Familial risk of multiple sclerosis: a nationwide cohort study*. *Am J Epidemiol.*, 2005. **162**(8): p. 774-8. Epub 2005 Aug 24. PubMed ID: 16120694.

First-degree relatives of Danish subjects with MS were found to have a seven times increased risk of MS compared with the general population. However, spouses of people with MS were not found to be at increased risk of MS.

- 34 J. Bertrams and E. Kuwert, *HLA antigen segregation analysis in multiple sclerosis (MS) families*. *Z Immunitätsforsch Immunobiol*, 1976. **152**(3): p. 200-8. PubMed ID: 1007375.

Segregation analysis performed in 38 families with a total of 52 people with MS showed a segregation of the haplotype A3-B7 toward MS subjects but not toward their healthy siblings. The haplotype A1-B8 was increased in both MS subjects and in their healthy siblings, raising the possibility that it confers protection against MS.

Terms searched in conjunction with “multiple sclerosis”:

inherit*
family/families/familial
concordance
twin
relative
sibling/brother/sister
parent/mother/father
child/offspring
adopt*
spouse/conjugal