# Parental transmission of MS in a population-based Canadian cohort

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## ABSTRACT

**Objective:** Genetic and environmental factors have important roles in multiple sclerosis (MS) susceptibility. The precise nature of these factors and mode of inheritance remains unknown. A female predominance is universally found. Recently, offspring of affected fathers were reported to be more likely to have MS than those of affected mothers. This was attributed to the Carter effect, which is seen in polygenic disorders. The Carter effect predicts that affected parents of the sex lesser affected by a disease/trait are more genetically loaded for risk alleles and thus transmit these more often to their offspring. This hypothesis was tested in a population-based Canadian MS cohort.

**Methods:** Using the longitudinal Canadian database, we identified 3,088 nuclear families with one affected parent and a total of 8,401 offspring, of which 798 had MS. Transmission to daughters and sons from affected mothers and fathers was compared.

**Results:** There was equal transmission of MS from affected fathers vs affected mothers (9.41% vs 9.76%). Stratifying by gender of affected parent there were no differences in the female:male sex ratio of affected (2.46% vs 2.41%, $p = 0.88$) or unaffected offspring (0.91% vs 0.95%, $p = 0.46$).

**Conclusions:** We observed[1] equal disease transmission to offspring from affected mothers and affected fathers,[2] no difference in the female:male sex ratio of affected offspring, and previously[3] no difference in sibling recurrence risk by gender of parent affected. These findings show no evidence for the Carter effect and do not support the hypothesis of polygenic inheritance of multiple sclerosis susceptibility by parent. ***Neurology*® 2007;69:1208–1212**

The etiology of multiple sclerosis (MS) is unknown. Several studies demonstrate the importance of genes in susceptibility.[1-3] More than 20% of MS cases are familial in Canada,[4] but the mode of inheritance is unknown.

Unequivocal association with MS has been shown with the MHC class II region.[5-8] Whole-genome linkage studies have shown variable evidence for other genomic regions[6,7,9-11] with few replications. These observations, as well as recurrence risks among first-degree relatives, provide support for a polygenic model of inheritance for MS. However, half-sib concordance[8] implies that this model will prove incorrect and unrecognized features of complexity may operate. The increasing preponderance of MS among females[12] implicates sexually dimorphic liability factors operating in MS susceptibility.

A recent report[13] concluded that the Carter effect exists in MS. This is a potentially important conceptual observation suggesting that MS inheritance follows the predicted gender-weighted oligogenic liability. The Carter effect was first described in pyloric stenosis[14] where females (least affected) transmit the disease more often than males. This was attributed to the greater genetic load needed for disease penetrance in females. Given

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**Table 1** Distribution of affected and unaffected offspring in families with affected mothers and fathers

| Families | Status | Total, n | Daughters, n (%) | Sons, n (%) | Female:male sex ratio |
|---|---|---|---|---|---|
| Maternal, n = 2,236 | Affected | 568 | 404 (71.13) | 164 (28.87) | 2.46 |
| | Unaffected | 5,254 | 2,558 (48.69) | 2,696 (51.31) | 0.95 |
| Paternal, n = 852 | Affected | 225 | 159 (70.67) | 66 (29.33) | 2.41 |
| | Unaffected | 2,165 | 1,034 (47.76) | 1,131 (52.24) | 0.91 |
| | Total | 8,212 | 4,155 (50.60) | 4,057 (49.40) | 1.02 |

the higher prevalence of MS in females, it was hypothesized that affected males had a higher genetic load and their offspring would be at a greater risk for MS. We evaluated transmission of MS susceptibility in a large Canadian population-based cohort by comparing disease transmission from affected fathers and mothers.

**METHODS** As part of the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS),[15] information has been collected for over 30,000 families. To investigate disease transmission from affected parents, we identified 4,921 pedigrees with confirmed MS cases, where at least one of the parents was affected. We studied those families with children born before 1980 to restrict analysis to offspring having at least reached the peak age at onset for MS.[16] Families with both parents affected (conjugal MS) were removed from the analysis (n = 19). Evaluation of disease transmission from affected parents was carried out by comparing the frequency of affected offspring born to affected fathers to the frequency of affected offspring born to affected mothers. Significance was assessed using Pearson $\chi^2$ (using Yates continuity correction for 1 *df* tests).

**RESULTS** Following the exclusion of conjugal MS families (n = 19) and families with offspring born after 1980 (n = 1,814), a total of 3,088 nuclear families were available for study. Of these, 2,236 had an affected mother (maternal families) and 852 had an affected father (paternal families). The total number of offspring from these families was 8,212 (median number of offspring per family = 2; range = 1 to 15; female:male sex ratio = 1.02) and 793/8,212 had MS (female:male sex ratio = 2.44). The female:male sex ratio of affected offspring from maternal and paternal families is shown separately in table 1.

The affected female:male sex ratio was no different in paternal vs maternal families (2.41% vs 2.46%, $p = 0.88$; OR = 1.02; 95% CI = 0.7281 to 1.4359). This was also seen in unaffected offspring (0.91% vs 0.95%, $p = 0.46$; OR: 1.04; CI = 0.9389 to 1.1472; see table 1). There were no differences in the distribution of paternal vs maternal sibship size (table 2).

When disease transmission to offspring from affected fathers was compared to transmission from affected mothers, no differences were found ($p = 0.63$, OR = 0.96, 95% CI 0.81 to 1.13). Similarly, no differences were observed when comparing transmission for daughters ($p = 0.79$, OR = 0.97, 95% CI 0.79 to 1.18) and sons ($p = 0.77$, OR = 0.95, 95% CI 0.71 to 1.28; table 3). We have also analyzed the data by adding those families previously excluded because of post 1980 births (n = 1,814) and the results are unchanged (data not shown).

**DISCUSSION** MS is a complex trait with an as yet unknown mode of inheritance. The Carter effect[14] describes a mechanism by which individuals of the less affected sex carry a higher genetic load and are thus more likely to transmit the trait/disease to their offspring. Recently, it has been suggested in MS that affected fathers are more likely to transmit MS compared to affected moth-

**Table 2** Distribution of maternal and paternal families by total sibship size (i.e., including affected and unaffected)

| Sibship size | Maternal families, n (%) | Paternal families, n (%) |
|---|---|---|
| 1 | 396 (17.73) | 145 (17.02) |
| 2 | 870 (38.94) | 296 (34.74) |
| 3 | 493 (22.07) | 202 (23.71) |
| 4 | 258 (11.55) | 98 (11.50) |
| 5 | 111 (4.97) | 62 (7.28) |
| 6 | 59 (2.64) | 26 (3.05) |
| 7 | 21 (0.94) | 9 (1.06) |
| 8 | 10 (0.45) | 6 (0.70) |
| 9 | 7 (0.31) | 3 (0.35) |
| 10 or more | 9 (0.40) | 5 (0.59) |


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**Table 3** Distribution of multiple sclerosis (MS) transmission from affected mothers and fathers to their offspring

| | Transmitted, n (%) | Not transmitted, n (%) | Total | *p* | OR | 95% CI |
|---|---|---|---|---|---|---|
| Transmission to all offspring | | | | | | |
| From father | 225 (9.41) | 2,165 (90.59) | 2,390 | 0.63 | 0.96 | 0.82 to 1.13 |
| From mother | 568 (9.76) | 5,254 (90.24) | 5,822 | | | |
| To daughters | | | | | | |
| From father | 159 (13.33) | 1,034 (86.67) | 1,193 | 0.79 | 0.97 | 0.79 to 1.18 |
| From mother | 404 (13.64) | 2,558 (86.36) | 2,962 | | | |
| To sons | | | | | | |
| From father | 66 (5.51) | 1,131 (94.49) | 1,197 | 0.77 | 0.96 | 0.71 to 1.29 |
| From mother | 164 (5.73) | 2,696 (94.27) | 2,860 | | | |

Only definite MS cases included. Affected parent n = 3,088 (852 paternal, 2,236 maternal).

ers.[13] This study concluded that increased paternal transmission was consistent with the Carter effect. The present study, utilizing a cohort over an order of magnitude larger than the previously published study, does not support their findings. Indeed, there is not a trend in the direction reported.

This investigation of the Carter effect was carried out in 197 nuclear families with one affected parent (146 affected mothers; 52 affected fathers; 45 affected offspring; 391 unaffected offspring). Primary analysis used cases with definite MS (n = 197 families) while a secondary analysis combined definite and possible MS cases (n = 255 nuclear families).[2] They found that among the definite MS cases, affected fathers transmitted MS to their offspring more often than affected mothers. This effect appeared to be independent of offspring sex. The secondary analysis which included both definite and possible MS followed the same trend but did not reach significance. The findings of this study, if correct, imply a polygenic mode of inheritance for MS, but the cohort used may not be immune to ascertainment bias.

In our Canadian cohort, we used only definite MS cases. We included families with one affected parent and studied affected offspring born before 1980. In a total of 3,088 families, we found no differences in the overall number or sex ratio of offspring born to affected mothers and fathers, nor did we observe differences in paternal vs maternal MS transmission. To address a possible effect caused by the sex of the offspring and to take into account the female preponderance in MS, transmission to daughters and sons was compared within maternal and paternal families. These comparisons showed that affected mothers and fathers were equally likely to transmit MS to their offspring.

Studies investigating parent-of-origin effects in MS concur that an affected parent increases risk for offspring.[17-20] The question of maternal vs paternal effect has produced what might be seen as conflicting evidence. A study of concordant parent-child pairs[19] did not observe any effect of the sex of the affected parent on the sex of affected offspring. Nonetheless, the study suggested slight affected parent effects on clinical features including an earlier age at onset to daughters of affected mothers and increased risk for primary progressive MS for sons of affected fathers. A recent Danish population-based study of absolute risks to relatives of patients with MS concluded that the gender-specific risk to relatives of male and female patients with MS was increased[20] but only as attributable to the gender variations in the background MS incidence. Of interest, an early Canadian study[26] tested goodness of fit of MS to the polygenic threshold model and this model was rejected.

Previous reports using parent-child cohorts from the CCPGSMS have examined factors related to increased sibling risk. A trend for increased sib recurrence risks among offspring of affected fathers was reported, although not formally significant.[17] A later report[18] concurred with the increased risk to the offspring of affected parents, but was underpowered to exclude an effect of sex of the affected parent. An increased risk to siblings of affected males was not observed as would be expected if the heritability conditions responsible for the Carter effect were operating in MS.

The much larger study reported here combined the families used in the previous CCPGSMS reports with 2,436 families not previously included. No distortion in disease transmission from affected mothers vs affected fathers was


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found. There appears to be a clear difference between transmission of risk from an affected parent compared to an unaffected parent, possibly providing an important clue to the modes of transmission of risk. To illustrate, concordant half-sib pairs from the CCPGSMS demonstrated a significant maternal effect[3] as do some unpublished twin data (Ebers and Sadovnick). However, influence on risk from each parental side was established recently.[27]

The drop in MS concordance from monozygotic to dizygotic twins,[21] as well as mathematical approximations based on recurrence risks,[22] have led to the assumption that many genes are involved in MS susceptibility. This has not been coherent with other comparisons. Given that the drop in concordance from full to half-siblings is contrary to expectation[3] and that genome-wide studies have failed to find consistent linkage other than to the MHC class II region,[6,7,23,24] this hypothesis is not on solid ground. We recently followed up all previous linkage hits in the Canadian samples and have suggested that the paradigm being used to justify and analyze further linkage searches may need rethinking.[24] Findings from a timing of birth study[25] as well as from the aforementioned half-sib study[3] imply that inheritance patterns of MS susceptibility are affected by environmental effects and potentially even by epigenetic processes. It has been shown that there has been a steady temporal increase in the female-to-male sex ratio in MS,[12] suggesting that female risk is more strongly influenced by the environment.

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## REFERENCES

1. Ebers GC, Sadovnick AD, Risch NJ. A genetic basis for familial aggregation in multiple sclerosis. Canadian Collaborative Study Group. Nature 1995;377:150–151.
2. Sadovnick AD, Ebers GC, Dyment DA, Risch NJ. Evidence for genetic basis of multiple sclerosis. The Canadian Collaborative Study Group. Lancet 1996; 347:1728–1730.
3. Ebers GC, Sadovnick AD, Dyment DA, Yee IM, Willer CJ, Risch N. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. Lancet 2004; 363:1773–1774.
4. Sadovnick AD, Ebers GC. Genetics of multiple sclerosis. Neurol Clin 1995;13:99–118.
5. Fogdell A, Hillert J, Sachs C, Olerup O. The multiple sclerosis- and narcolepsy-associated HLA class II haplotype includes the DRB5*0101 allele. Tissue Antigens 1995;46:333–336.
6. Dyment DA, Sadovnick AD, Willer CJ, et al. An extended genome scan in 442 Canadian multiple sclerosis-affected sibships: a report from the Canadian Collaborative Study Group. Hum Mol Genet 2004;13: 1005–1015.
7. Sawcer S, Ban M, Maranian M, et al. A high-density screen for linkage in multiple sclerosis. Am J Hum Genet 2005;77:454–467.
8. Lincoln MR, Montpetit A, Cader MZ, et al. A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. Nat Genet 2005;37:1108–1112.
9. Ebers GC, Kukay K, Bulman DE, et al. A full genome search in multiple sclerosis. Nat Genet 1996;13:472–476.
10. Akesson E, Oturai A, Berg J, et al. A genome-wide screen for linkage in Nordic sib-pairs with multiple sclerosis. Genes Immun 2002;3:279–285.
11. Kuokkanen S, Gschwend M, Rioux JD, et al. Genome-wide scan of multiple sclerosis in Finnish multiplex families. Am J Hum Genet 1997;61:1379–1387.
12. Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006;5:932–936.
13. Kantarci OH, Barcellos LF, Atkinson EJ, et al. Men transmit MS more often to their children vs women: the Carter effect. Neurology 2006;67:305–310.
14. Carter CO. Inheritance of Congenital Pyloric Stenosis. Br Med Bull 1961;17:251–254.
15. Sadovnick AD, Risch NJ, Ebers GC. Canadian collaborative project on genetic susceptibility to MS, phase 2: rationale and method. Canadian Collaborative Study Group. Can J Neurol Sci 1998;25:216–221.
16. Paty D, Ebers G. Multiple Sclerosis. Philadelphia: F.A. Davis Company; 1998.
17. Sadovnick AD, Yee IM, Ebers GC, Risch NJ. Effect of age at onset and parental disease status on sibling risks for MS. Neurology 1998;50:719–723.
18. Sadovnick AD, Yee IM, Ebers GC. Factors influencing sib risks for multiple sclerosis. Clin Genet 2000;58:431–435.
19. Hupperts R, Broadley S, Mander A, Clayton D, Compston DA, Robertson NP. Patterns of disease in concordant parent-child pairs with multiple sclerosis. Neurology 2001;57:290–295.
20. Nielsen NM, Westergaard T, Rostgaard K, et al. Familial risk of multiple sclerosis: a nationwide cohort study. Am J Epidemiol 2005;162:774–778.
21. Willer CJ, Dyment DA, Risch NJ, Sadovnick AD, Ebers GC. Twin concordance and sibling recurrence rates in multiple sclerosis. Proc Natl Acad Sci USA 2003;100:12877–12882.



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22. Lindsey JW. Familial recurrence rates and genetic models of multiple sclerosis. Am J Med Genet A 2005; 135:53–58.
23. Kenealy SJ, Herrel LA, Bradford Y, et al. Examination of seven candidate regions for multiple sclerosis: strong evidence of linkage to chromosome 1q44. Genes Immun 2006;7:73–76.
24. Herrera BM, Cader MZ, Dyment DA, et al. Follow-up investigation of 12 proposed linkage regions in multiple sclerosis. Genes Immun 2006;7: 366–371.
25. Willer CJ, Ebers GC. Susceptibility to multiple sclerosis: interplay between genes and environment. Curr Opin Neurol 2000;13:241–247.
26. Sadovnick AD, Spence MA, Tideman S. The goodness of fit for the polygenic threshold model: application to multiple sclerosis. Am J Med Genet 1981;8: 355–361.
27. Dyment DA, Herrera BM, Cader MZ, et al. Complex interactions among MHC haplotypes in multiple sclerosis: susceptibility and resistance. Hum Mol Genet 2005;14:2019–2026.

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