

MHC transmission: Insights into gender bias in MS susceptibility.

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Abstract

OBJECTIVE: Major histocompatibility complex (MHC) genes dominate genetic susceptibility factors in multiple sclerosis (MS). Given the general consensus that incidence and prevalence of MS has been rising and specifically in women, we evaluated MHC-gender interactions.

METHODS: In a large family-based cohort consisting of 7,093 individuals (2,127 affected individuals) from 1,055 MS families, we examined MHC transmission by family structure and gender stratified by genetic distance of affected relatives from the MS proband.

RESULTS: We found that affected individuals with HLA-DRB1*15-positive genotypes have higher female-to-male ratios as compared with affected individuals with HLA-DRB1*15-negative genotypes ($\chi^2 = 9.97$, $p = 0.0015$) with the exception of multiplex families with 3 or more affected across 2 generations. Transmission disequilibrium test results show that HLA-DRB1*15 transmission was more distorted in collateral families vs nuclear families ($\chi^2 = 8.030$, $p = 0.0046$), exclusively in affected female-female pairs ($\chi^2 = 7.81$, $p = 0.0051$), but not in mixed gender pairs ($\chi^2 = 1.58$, $p = 0.21$) or matched male pairs (Fisher $p = 0.21$).

CONCLUSIONS: These observations implicate the MHC as the site of interactions and modifications mediating the female-to-male gender ratio in MS and its progressive increase. They further suggest this occurs via gene-environment interactions and epigenetic modifications in this region. The difference between collateral and nuclear families provides some insight into the inheritance, decay, and gender specificity of putative epigenetic marks.

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Gene Study Suggests Why MS Is Women's Disease

[This report is part of a 12-month Clinical Context series.](#)

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Action Points

- Explain to interested patients that this study shows there may be a genetic cause for female predominance in multiple sclerosis.

The mystery of why multiple sclerosis predominantly strikes women may have been unraveled a bit, thanks to a new genetic study.

Polymorphisms in major histocompatibility complex (MHC) genes and their associated DNA methylation patterns may combine with environmental influences in ways that promote greater susceptibility to the disease in women than in men, according to George C. Ebers, MD, FMedSci, of John Radcliffe Hospital in Oxford, England, and colleagues.

Published online in *Neurology*, their findings were based on genomic analyses of more than 7,000 members of 1,055 families affected by MS.

Ebers and colleagues noted that, 100 years ago, MS was reported to affect men and women about equally.

However, in their sample, of the more than 2,100 individuals who had MS, 73% were female. They noted that published reports from around the world point to an approximate 2:1 ratio of female versus male MS patients.

MS risk is believed to have a strong heritable component centered on MHC genes, but the reason for the female predominance has been unclear. Previous studies have ruled out genes carried on the X chromosome as contributing significantly to MS.

Consequently, Ebers and colleagues sought to identify genetic or epigenetic factors related to MHC genes elsewhere in the genome that might also have discrepant associations with gender.

The study showed that, depending on how the family members were related, and on the genotype for a particular MS-associated MHC gene, the female-to-male ratio of those with the disease differed markedly.

The female predominance was particularly great when affected members of families had the *HLA-DRB1*15* genotype.

There were also considerable differences in transmission of the

genotype from one generation to the next according to the relationships between affected members.

When member pairs were related more directly -- parent-child or sibling-sibling -- the odds of transmission across generations appeared lower than when the family structure was "collateral," related as aunts-uncles-nieces-nephews or as cousins.

Within nuclear families, the odds ratio for *HLA-DRB1*15* transmission was 2.12, compared with 3.35 for the collateral families ($P=0.0046$ for the comparison).

The odds of transmission also were greatest in both family types when affected relative pairs were both female.

The findings, according to Ebers and colleagues, suggest that "differential transmission of the same haplotype in families with affected first-degree relatives versus those consisting of second- and third-degree relatives reflects the inheritance of putative epigenetic marks."

The researchers suggested that DNA methylation -- which can be affected by environmental factors and is heritable -- could be the "epigenetic mark" responsible for these effects, although they acknowledged that supporting experimental data were still lacking.

In an accompanying editorial, a Mayo Clinic researcher pointed out that epigenetics provide the only plausible mechanism that could account for the onset of female predominance in MS.

"Given the rapidity of increase in the sex ratio, there does not seem to be enough evolutionary time to spread a purely genetic risk, and therefore [genomic-environmental interaction] seems to be the more likely explanation," wrote Orhun Kantarci, MD, of Mayo's branch in Rochester, Minn.

Ebers and colleagues noted that MHC genes are believed to be the primary genetic drivers of other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, that also affect far more women than men.

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Ebers reported relationships with Roche, UCB, and Bayer Schering. Another author reported relationships with Bayer Canada, Teva, EMD Serono, and Biogen Idec. Other authors indicated they had no financial relationships with commercial entities.

Kantarci reported research support from the Hilton Foundation and other nonprofit

organizations.
