



## **Analysis of genetic mutations or alleles on the X or Y chromosome as possible causes of Multiple Sclerosis**

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### **Summary**

Diseases involving the sex chromosomes (X and Y) often exhibit distinctive gender biases and inheritance patterns. Although the observed 2:1 female:male ratio in MS suggests a possible sex chromosome involvement, other evidence indicates that X and/or Y genes are not solely responsible for MS. However, it is certainly possible that genes on these chromosomes contribute to MS risk in a polygenic fashion. A few studies have examined X chromosome loci for possible involvement in MS, but no locus has yet been confirmed. No Y chromosome loci have yet been examined. More detailed examination of both chromosomes is required to determine their contribution to the etiology of MS.

Note: A spreadsheet compiling relevant details of the published candidate gene studies and genome screens conducted for MS can be found in the file *phase2-genetic-studies.xls* available for download at [www.acceleratedcure.org](http://www.acceleratedcure.org).

### **Hypothesis**

Mutations to or alleles of genes located on the X or Y chromosome either cause MS or influence susceptibility to MS.

### **Experimental tests of the hypothesis**

Population and inheritance studies analyzing gender distributions in MS have yielded some clues about the potential for susceptibility genes to be located on either the X or Y chromosome<sup>1-3</sup>. The existence of females with MS is evidence that the disease is not caused solely by a pathogenic defect on the Y chromosome, just as the existence of father-son concordant pairs implies that MS is not caused solely by an inherited genetic defect on the X chromosome.

Even if MS is not an X- or Y-linked Mendelian disease, the possibility remains that it is a polygenic disease with susceptibility genes located on the X or Y chromosome. One attempt to fit various oligogenic models to available inheritance data found that the best fit was provided by a hypothesis involving a recessive autosomal gene and a dominant X chromosome gene<sup>4</sup>. While other analyses have produced different genetic models for MS, the involvement of an X-linked dominant genetic mutation in MS might partially account for the observed female bias. However, the influence of an MS susceptibility

gene on the X chromosome might be limited as indicated by a study of X inactivation patterns in monozygotic twins. The study was unable to link discrepancies in X inactivation patterns to discordance for MS in monozygotic twins, suggesting that X-linked genes do not play a predominant role in determining risk for MS<sup>5</sup>. Another study also could not find excess skewing of X chromosome inactivation in female subjects with a variety of autoimmune diseases including MS<sup>6</sup>. However, the authors suggest that X inactivation skewing in certain cell populations, such as thymic dendritic cells, may lead to a situation of self-intolerance. Furthermore, subsequent studies of autoimmune thyroiditis and scleroderma did find associations with X inactivation skewing in these diseases<sup>7-9</sup>.

Regarding the search for susceptibility genes, several candidate gene studies and genomewide screens have explored possible associations between X chromosome loci and MS (no such studies have yet been reported for the Y chromosome). Four X chromosome genes have been the focus of candidate gene studies: proteolipid protein (PLP, located on Xq22), interleukin 2 receptor gamma (IL-2R gamma, Xq13.1), CD40 ligand (Xq26), and gamma-aminobutyric acid ionotropic type A (GABA-A) receptor (GABRA3, Xq28). PLP has been studied three times, with no association found, and IL-2R gamma and CD40 ligand have each been studied once, also with negative results. The single study examining GABRA3 did produce evidence for association but this has not yet been confirmed. No published results appear to be available regarding involvement of the gene for the demyelinating disease X-linked adrenoleukodystrophy (ALD, Xq28) in people with MS.

Of the loci highlighted in genomewide screens, the Xp11 region is perhaps the most noteworthy, having been identified by six different studies as well as a meta-analysis of genomewide screens for autoimmune diseases.

One final study involving the X chromosome, a cytogenetic analysis of MS subjects, found that 50% had aberrations of the X chromosome, such as premature centromere division, translocations or deletions<sup>10</sup>. It is not known what the significance of this finding might be, nor whether these aberrations were the result of disease activity rather than a cause.

## Conclusions

MS is not caused solely by a mutation in the X or Y chromosome (that is, MS is not a Mendelian X-linked or Y-linked disorder). However, it is possible that one or more loci on the X or Y chromosome influence susceptibility in at least some people with MS. A few genetic studies have analyzed loci on the X chromosome for potential association with MS, but these have been too few in number to produce conclusive results. No studies have yet been performed of loci on the Y chromosome, so it is still unknown what contribution, if any, it makes to the development of the disease.

## References

Note: The spreadsheet *phase2-genetic-studies.xls* contains the PubMed ID of all candidate gene and genome screen studies which were included in this analysis.

- 1 A. D. Sadovnick, D. Bulman and G. C. Ebers, *Parent-child concordance in multiple sclerosis*. *Ann Neurol*, 1991. 29(3): p. 252-5. PubMed ID: 2042941.  
75 parent-child pairs concordant for MS included 40 mother-daughter pairs, 13 mother-son pairs, 21 father-daughter pairs, and 1 father-son pair. The authors conclude that the data show a paucity of father-son pairs.
- 2 M. P. Roth, J. Clayton, E. Patois and A. Alperovitch, *Gender distributions in parents and children concordant for multiple sclerosis*. *Neuroepidemiology*, 1994. 13(5): p. 211-5. PubMed ID: 7969704.  
170 parent-child pairs included 72 mother-daughter pairs, 48 mother-son pairs, 37 father-daughter pairs and 13 father-son pairs, consistent with the observed 2:1 female:male ratio.
- 3 R. Hupperts, S. Broadley, A. Mander, D. Clayton, D. A. Compston and N. P. Robertson, *Patterns of disease in concordant parent-child pairs with multiple sclerosis*. *Neurology.*, 2001. 57(2): p. 290-5. PubMed ID: 11468314.  
Clinical phenotype of MS was studied in a cohort of 245 affected parent-child pairs. Possible parent of origin effects were found for disability, disease course, and risk of having additional affected offspring.
- 4 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.  
Various oligogenic models were tested against the available MS inheritance data. The best fitting hypothesis stated that MS occurs in people homozygous for a recessive autosomal gene and possessing a dominant X gene, both with reduced penetrance.
- 5 V. Trejo, C. Derom, R. Vlietinck, W. Ollier, A. Silman, G. Ebers, R. Derom and P. K. Gregersen, *X chromosome inactivation patterns correlate with fetal-placental anatomy in monozygotic twin pairs: implications for immune relatedness and concordance for autoimmunity*. *Mol Med*, 1994. 1(1): p. 62-70. PubMed ID: 8790602.  
In a study of 26 female monozygotic twin pairs with MS or rheumatoid arthritis, X inactivation patterns did not distinguish between twin pairs who were concordant or discordant for either disease.
- 6 S. Chitnis, J. Monteiro, D. Glass, B. Apatoff, J. Salmon, P. Concannon and P. K. Gregersen, *The role of X-chromosome inactivation in female predisposition to autoimmunity*. *Arthritis Res*, 2000. 2(5): p. 399-406. PubMed ID: 11056674.  
A comparison of X chromosome inactivation patterns in women with autoimmune disease and normal controls did not detect any differences between the two groups.
- 7 T. Ozcelik, E. Uz, C. B. Akyerli, S. Bagislar, C. A. Mustafa, A. Gursoy, N. Akarsu, G. Toruner, N. Kamel and S. Gullu, *Evidence from autoimmune thyroiditis of skewed X-chromosome inactivation in female predisposition to autoimmunity*. *Eur J Hum Genet.*, 2006. 14(6): p. 791-7. PubMed ID: 16596118.

Skewed X chromosome inactivation was found in a higher proportion of women with autoimmune thyroid disease compared with healthy controls. This phenomenon was observed in peripheral blood cells, as well as buccal mucosa and (to a lesser degree) thyroid tissue.

- 8 T. H. Brix, G. P. Knudsen, M. Kristiansen, K. O. Kyvik, K. H. Orstavik and L. Hegedus, *High frequency of skewed X-chromosome inactivation in females with autoimmune thyroid disease: a possible explanation for the female predisposition to thyroid autoimmunity*. J Clin Endocrinol Metab., 2005. 90(11): p. 5949-53. Epub 2005 Aug 16. PubMed ID: 16105963.

A study of female twins with and without autoimmune thyroid diseases found a higher frequency of skewed X chromosome inactivation in the twins with thyroid disease compared with the healthy twins.

- 9 Z. Ozbalkan, S. Bagislar, S. Kiraz, C. B. Akyerli, H. T. Ozer, S. Yavuz, A. M. Birlik, M. Calguneri and T. Ozcelik, *Skewed X chromosome inactivation in blood cells of women with scleroderma*. Arthritis Rheum., 2005. 52(5): p. 1564-70. PubMed ID: 15880831.

Skewed X chromosome inactivation in peripheral blood DNA was found in 64% of female subjects with scleroderma compared with 8% of female controls, and extreme skewing was found in 49% of the scleroderma subjects compared with 2% of controls. No differences in inactivation were found between the groups for skin biopsy samples.

- 10 E. D'Alessandro, M. Di Cola, M. L. Lo Re, C. Ligas, C. Vaccarella, F. D'Andrea, C. Marini and M. Prencipe, *Nonrandom chromosome changes in multiple sclerosis*. Am J Med Genet, 1990. 37(3): p. 406-11. PubMed ID: 2260573.

Cytogenetic analysis of 48 subjects with clinically definite MS showed that 50% had abnormal chromosomes, showing premature centromere division of the X chromosome and structural aberrations, translocations, or deletions that could suggest preferential breakpoints. Cytogenetic abnormalities were more common in subjects with high frequency of relapse or with progressive MS.

#### **Terms searched in conjunction with “multiple sclerosis”:**

X chromosome  
Y chromosome  
genome screen  
“gene” with:  
proteolipid protein  
interleukin 2 receptor  
adrenoleukodystrophy  
GABRA3  
CD40 ligand