



## **Analysis of genotypes that alter RNA expression as a possible cause of Multiple Sclerosis**

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### **Summary**

The genetic variant or variants that help determine susceptibility to a disease may do so by altering the structure of the proteins they encode, or by altering the expression of these proteins. Many studies have demonstrated underexpression and overexpression of various proteins in people with MS compared with controls, raising the possibility that expression-altering genetic variants are associated with MS. However, to date no conclusive evidence has been produced linking risk of MS with differential protein expression resulting from a genetic variant.

### **Hypothesis**

Genetic defects or variants that directly alter or influence gene expression increase susceptibility to MS.

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

One of the ways in which a genetic variant can lead to a disorder is through increasing or decreasing the quantity produced of a particular protein. For example, a gene duplication may lead to higher levels of a protein while a mutation that results in an unstable protein may result in lower levels of that protein. Mutations in promoter regions of genes or epigenetic factors such as improper methylation can also lead to over- or underexpression.

Many experiments have measured gene transcription or protein expression levels in MS in an attempt to better understand the pathogenesis of the disease. These range from studies examining individual candidate proteins (particularly immune or inflammatory cytokines) proposed to play a role in MS to microarray studies that examine up to thousands of genes using a single specimen.

These studies have identified a wide range of genes that appear to be expressed differently in MS. For example, one study found increased expression of the chemokines CXCR3 and CCR5 in MS subjects compared with controls<sup>1</sup>. Another demonstrated the upregulation of the apoptosis mediators cFLIP, caspase-8, CD95 and

CD95L in peripheral blood cells of MS subjects compared with controls<sup>2</sup>. However, the discovery that a particular gene is over- or underexpressed in MS does not necessarily mean that a genetic variation is the underlying cause. The differential expression could also result from environmental or epigenetic factors that are present in the disease. For instance, cytokines can be up- or downregulated by inflammatory or regulatory molecules, proteins involved in myelination may be upregulated by growth factors present in the central nervous system, and so on. Therefore, proving that a genetic variant is the basis for a differentially expressed gene in MS requires not just demonstrating the change in expression but also finding a genetic variant that is associated with altered expression and showing that this variant is associated with MS.

Two types of approaches have been taken to identify expression-altering genetic variants involved in MS. One approach is to perform linkage or association studies on genes whose proteins have been found to be over- or underexpressed in MS. Many candidate gene studies of inflammatory or immunomodulatory proteins have been motivated by protein expression results. Examples of these studies include:

- A sequencing of the IFN-gamma promoter region and first intron for possible mutations that may result in the altered expression seen in MS; one promoter region point mutation was found but it was present only at a very low frequency in the study population<sup>3</sup>.
- A case-control study analyzing a microsatellite marker found in the PECAM-1 gene, which was prompted by increased PECAM-1 levels found in the serum of MS subjects with active lesions; no significant association was demonstrated in this study<sup>4</sup>.
- The finding of increased levels of osteopontin in MS brain tissue in a microarray analysis has spurred interest in this protein as a potential contributor to MS. Since this study was published, five MS genotyping studies have investigated the osteopontin gene. Two studies found a significant difference between MS subjects and controls for an allele or haplotype<sup>5,6</sup> while the others found no differences for any of the alleles tested<sup>7-9</sup>.

The results noted above are illustrative of the overall level of success of candidate gene studies in MS to date. Most genes studied in MS have either produced generally negative results (as in PECAM-1, for which four studies have failed to find any association) or mixed results (as in the case of the five osteopontin studies cited above or the twelve IFN-gamma studies performed to date).

The other approach that is used to find expression-altering genetic variants in MS is the analysis of alleles already associated with differential regulation to investigate possible association with MS. Indeed, knowledge that an allele known to influence the expression of a gene increases susceptibility to MS would be very valuable for understanding the pathogenesis of MS and developing new treatments. Unfortunately, none of the alleles studied in this manner have to date been definitively linked with MS (see Table 1 below). Several of these alleles have only been studied once or twice. For others, multiple studies have been performed but with negative or inconsistent results. Inconsistent results may be due to issues with the performance of one or more of the studies (e.g., the use of insufficient numbers of subjects), or to possible genetic heterogeneity whereby the gene plays a role only in a subset of people with MS.

Table 1. Gene regulation-associated alleles studied for linkage or association with MS

<b>Gene name</b>	<b>Allele studied for linkage/association with MS</b>	<b>Results of studies</b>
Alpha-1-antitrypsin	Variety of alleles such as substitutions and premature stop codons leading to unstable proteins	Of the two studies performed, one found an increased frequency of the normal allele M3 in MS subjects <sup>10</sup> while the other found no association <sup>11</sup>
Apo-1/FAS	Promoter region SNP at position -670 that may disrupt a transcription element binding site	Four studies offer mixed results <sup>12-15</sup>
Apolipoprotein E (APOE)	Promoter region SNP at -419 that may alter transcription	Only one study has been performed to date <sup>16</sup>
ASA	ASA pseudodeficiency allele, which causes a deficiency of a certain mRNA species	Only one study has been performed to date <sup>17</sup>
Blood group Rh	Deletion of the Rh gene (people who are Rh-negative are homozygous for this deletion)	Four studies have been performed, offering mixed results <sup>18-21</sup>
CCL5	SNP at position -471 that creates a new transcription factor binding site	A trend toward association was found in DR15- negative MS cases in one study <sup>22</sup>
CCR5	Delta 32 mutation which creates a frameshift resulting in premature termination of translation	Seven studies found no role for this mutation as a cause of MS <sup>23-29</sup> ; however, other studies identified an association with MS <sup>30</sup> , with PPMS <sup>31</sup> , or with MS in combination with HLA alleles (e.g., DR4) <sup>32, 33</sup>
CD24	CD24v SNP that increases cell surface expression of CD24	Two studies found an association with the v/v genotype for MS <sup>34, 35</sup> ; however, a third found this genotype to be underrepresented in MS cases <sup>36</sup>
Ciliary neurotrophic factor	G/A null mutation at position -6 of exon 2	Two studies found similar frequencies of the mutation in cases and controls <sup>37, 38</sup>
Complement component 4A	Null allele C4AQ0	Two studies suggest an association of this allele with MS <sup>39, 40</sup>
CTLA-4	SNPs in the promoter region and in exon 1, both associated with altered expression	Evidence for association with the exon 1 +49G allele was found in six studies <sup>33, 41-45</sup> but not twelve others <sup>31, 46-56</sup> ; seven studies found no link between MS and promoter region -318 SNP <sup>41-43, 48, 49, 53, 57</sup> ; two studies found an association for haplotypes including both SNPs <sup>58, 59</sup>
CYP2D6	Various deletions and duplications which result in decreased or absent expression	The only study performed to date did not identify significant differences between MS subjects and controls <sup>60</sup>
Gelatinase B	Promoter region SNP and microsatellite that have been associated with altered expression levels	Two studies show no evidence of influence on MS risk <sup>61, 62</sup> ; however, a third study found an association between higher microsatellite repeat numbers and MS <sup>63</sup>
Glutathione S-transferase supergene	Deletions of the genes GSTT1 and GSTM1	Neither of these deletions were associated with MS in a study of GST genes <sup>64</sup> ; in addition, no association was

family		found between GSTM1 genotype and organic solvent exposure in a group of MS subjects <sup>65</sup>
ILT6 (LILRA3)	Large deletion that results in non-expression of gene	One study showed that ITL6 homozygous deficiencies were more prevalent in MS cases compared with controls <sup>66</sup>
Interferon gamma	An intron 1 SNP (+874) associated with gene expression (also in linkage disequilibrium with a CA repeat microsatellite)	Several studies have examined this locus; most have reported no evidence for linkage or association <sup>67-74</sup>
Interleukin-1 alpha	SNP at position –889 that has been associated with gene regulation	No study has yet associated this variant with MS <sup>57, 75, 76</sup>
Interleukin-1 beta	Taq I restriction fragment length polymorphism in exon 5 at position +3953, which influences production	Seven studies have been performed, all reporting no evidence for association with MS <sup>56, 75-80</sup>
Interleukin-1 receptor antagonist	Variable repeat allele in one intron which has been linked to increased production of IL-1ra	Thirteen studies have been performed, of which four reported conflicting associations <sup>56, 81-83</sup> , eight reported no association <sup>76-80, 84-86</sup> , and one reported tentative association in women <sup>75</sup>
Interleukin-4	SNP at position 33 (C/T) that is in linkage disequilibrium with a functionally significant promoter SNP at -590	Of the four investigations of these SNPs, three found no association with MS <sup>57, 87, 88</sup> , while one reported a protective role for the heterozygous +33 genotype <sup>89</sup>
Interleukin-6	Minisatellite polymorphism in the 3' flanking region and SNP at position –174 in the promoter region, both of which potentially influence expression	None of six studies found evidence for a role for these variants in susceptibility to MS <sup>57, 73, 90-93</sup>
Interleukin-8	-251 A/T polymorphism that affects gene expression	MS was found in one study to be associated with the low producer genotype T/T <sup>94</sup>
Interleukin-10	A->G substitution at position –1082 and microsatellite markers in the promoter region associated with altered expression	Seven studies found no association of these variants with MS <sup>31, 73, 95-99</sup> , tentative evidence for involvement of one microsatellite marker was found in one study <sup>100</sup>
Interleukin-12 p40	SNP in the 3' untranslated region of the gene which has been linked to production	One study showed a significant protective effect for the BB (low-producer) genotype <sup>101</sup> ; however, three other studies failed to find a significant association <sup>99, 102, 103</sup>
Interleukin-13	Polymorphism at position -1024 which promotes binding of nuclear proteins to the promoter region	One study found no association with MS for this polymorphism <sup>104</sup>
Interleukin-18	Two promoter region SNPs at positions –607 and –137, with possible influences on production	Only one study has been conducted; it showed no significant differences in allele frequencies between cases and controls <sup>105</sup>
Leukemia	SNP at position +3951 that may	The only study that has been conducted

inhibitory factor (LIF)	reduce mRNA stability and affect expression	for this SNP in MS did not show an association <sup>106</sup>
Lymphotoxin alpha	Variant in exon 3 which is associated with reduced production of LTa	Only one study has been performed, which showed no direct association of the variant with MS but a possible association for an LTa/TNF genotype <sup>107</sup>
MCP-1 (CCL2)	Promoter region SNP –2518 A/G that increases expression	Neither of two studies found evidence of an association with MS for this SNP <sup>22, 108</sup>
Myeloperoxidase	Promoter region point mutation (-463 A/G) which appears to alter expression	Two studies detected an association between the higher-expressing genotype and MS <sup>109, 110</sup> , but two other studies failed to find an association <sup>4, 111</sup>
NOS2A	[CCTTT] repeat polymorphism in promoter region that influences expression	Of three studies analyzing this polymorphism, two found no evidence for linkage or association <sup>112, 113</sup> , while the third found modest evidence of linkage <sup>57</sup>
NRAMP1	Promoter region locus encoding Z-DNA-forming dinucleotides; four alleles have been identified which appear to have different effects on expression	One study has been conducted to date which showed a statistically significant distribution of alleles between MS subjects and controls <sup>114</sup>
Osteopontin	Haplotype of four polymorphisms that has been associated with OPN production	One study associated the higher-production haplotype with increased risk of MS <sup>6</sup> ; however, four others studying the individual alleles produced mixed results <sup>5, 7-9</sup>
Plasminogen activator inhibitor 1	4G/5G polymorphism in the promoter region reported to affect expression	One study showed the low-producing 5G/5G genotype to be associated with MS in women <sup>115</sup> ; however another study failed to replicate this association <sup>116</sup>
Prolactin	G/T SNP at position –1149; the G allele appears to increase promoter activity	Only one study has been performed, which showed no association for either allele with MS <sup>117</sup>
Protein-tyrosine phosphatase receptor-type C	C/G point mutation at position 77 in exon 4, which increases expression of isoform CD45RA	Three studies offer support for association with MS <sup>118-120</sup> ; however, six others show no increased frequency in subjects with MS <sup>121-126</sup>
Selectin P ligand	Met62Ile SNP that influences SELPLG plasma levels	An association found with MS in an Italian population could not be replicated in a British cohort <sup>127</sup>
SH2D2A	Polymorphic GA repeat in the promoter region	One study showed that short alleles (GA(13-16)), which are linked with lower expression of TSA <sub>d</sub> , were more common in MS subjects vs. controls <sup>128</sup>
TGF-beta 1	Three point mutations that have been reported to affect gene expression (-509 C/T, +869 T/C, and +915 G/C)	Five studies of these SNPs have produced mixed results <sup>33, 57, 73, 129, 130</sup>
Tumor necrosis factor alpha	Three point mutations in the promoter region (G/A SNP at position –308 (TNF2 mutation), G/A SNP at position –376, and G/A SNP at position –238) that	One study found a higher frequency of TNF2 in MS subjects vs. controls <sup>131</sup> ; another study found TNF2 more prevalent in controls <sup>132</sup> ; fourteen other studies found no significant differences

	are thought to influence gene expression.	either way <sup>31, 57, 73, 99, 107, 133-141</sup> Two Spanish studies found an association between TNF -376 and MS <sup>142, 143</sup> , while studies of American and Dutch populations found no correlation <sup>144, 145</sup> One study of nursing home residents found a higher frequency of the -238 GG genotype <sup>135</sup> ; however, several other studies have found no evidence for association <sup>57, 138-142, 145</sup> The triallelic combination -238 TNF*B1, -308 TNF*A2, CTLA4*G was found to distinguish MS cases from controls in one study <sup>33</sup>
Uncoupling protein 2	-866G allele that is associated with lower UCP2 expression	The only study that has studied this gene found the G allele to be overrepresented in MS subjects <sup>146</sup>

## Conclusions

Numerous proteins have shown to be over- or underexpressed in one or more tissues in MS patients compared with controls, and the increasing use of expression microarray technologies promises that many more will be identified in the future. While most of these cases of differential regulation are likely due to environmental or epigenetic factors present in MS, it is possible that some result from an underlying genetic variant that affects transcription. Candidate gene studies motivated by gene expression findings and investigations of alleles associated with altered transcription have both been performed in MS, but so far these have not resulted in the conclusive finding of an MS susceptibility gene.

## References

Note: Details for each of the MS candidate gene studies listed here can be found in the file *phase2-genetic-studies.xls* available for download at [www.bostoncure.org](http://www.bostoncure.org).

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