Colony stimulation factor 1 receptor (*CSF1R*) is not a common cause of multiple sclerosis

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Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is a rare autosomal dominant disorder characterized by cerebral white-matter degeneration. The onset of disease is typically in the fourth decade of life, and involves psychiatric, neurological and somatic symptoms leading to progressive cognitive and motor dysfunction [1, 2]. In magnetic resonance imaging (MRI), HDLS initially appears as patchy asymmetrical abnormalities in cerebral white-matter that become confluent and symmetrical as the disease progresses [3]. A definite diagnosis of HDLS relies on widespread loss of myelin sheaths and axonal degeneration, neuronal spheroids, gliosis and accumulation of lipid-laden macrophages at pathological examination [1].

Missense, frame-shift and splice-site mutations in colony stimulation factor 1 receptor (*CSF1R*) have been recently identified as the cause of HDLS [4]. Although the pathological presentation was consistent with HDLS, the clinical presentation was found to include multiple sclerosis (MS), Parkinson's disease, Alzheimer's disease, or frontotemporal dementia. Interestingly, a recent study identified three patients diagnosed with MS harboring *CSF1R* mutations [5].

MS is an inflammatory disease of the CNS characterized by myelin loss, varying degrees of axonal injury, and progressive neurological dysfunction. Due to the clinical and pathological overlap between MS and HDLS, the clinical diagnosis of MS in patients with *CSF1R* mutations [4, 5], and the biological role of *CSF1R* in the inflammatory response; we evaluated whether mutations in *CSF1R* are implicated in the pathological mechanisms necessary to trigger the onset of MS (Methods are provided as supplemental information).

Genetic characterization of the entire coding sequence of *CSF1R* in 95 probands diagnosed with MS did not identify any of the previously reported pathogenic variants for HDLS [4, 5]. Similarly, novel coding substitutions, frame-shifts or splice-site mutations were not

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observed. Detailed information for twelve previously reported *CSF1R* coding variants identified in this study, five missense and seven silent, is provided in Table 1. Minor allele frequencies for these variants were consistent with those previously reported in healthy controls, suggesting they are unlikely to have an effect on MS risk.

The identification of *CSF1R* pathogenic mutations in HDLS [4] suggested the possibility that this gene could be implicated in other more common white-matter disorders including MS. Additional support for this hypothesis was provided by the identification of *CSF1R* mutations in patients clinically diagnosed with MS [5]. However, despite the clinical and pathological overlap between HDLS and MS, sequencing of *CSF1R* in MS patients failed to identify any of the previously described HDLS mutations or novel mutations with potentially pathogenic effects. Although we could not confirm the presence of *CSF1R* mutations in a relatively small sample of MS patients, further studies in larger cohorts of MS patients, as well as other degenerative white-matter diseases, are warranted.

In conclusion, our study indicates that pathogenic mutations in *CSF1R* are an unlikely cause of MS in the Canadian population.

Supplementary Material

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Table 1

Coding variants identified in MS patients

rs number	Nucleotide	Amino Acid	Minor allele frequency
rs216123	T>C	P28P	0.45
rs56048668	T>G	V32G	0.02
rs41287102	C>T	S94S	0.01
rs17652007	C>T	H98H	0.01
rs2228422	C>T	T242T	0.48
rs146406037	A>T	N255I	0.01
rs149168939	G>A	R294Q	0.01
rs10079250	A>G	H362R	0.08
rs34951517	G>A	G413S	0.03
rs56327604	C>G	L845L	0.04
rs41287094	C>T	F903F	0.02
rs41287092	T>C	G933G	0.01