

**gMS-Classifier1 does not predict disability progression in multiple sclerosis**

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Several clinical, immunological and radiological biomarkers have been shown to predict the disease course of multiple sclerosis (MS).<sup>1-5</sup> One potential serum marker is the gMS-Classifier1, which is composed of IgM anti-Glc antibodies, namely anti-GAGA 2,3,4 and 6. Previous work demonstrated that the gMS-Classifier1 could not predict early conversion to clinically definite MS in a cohort of clinically isolated syndrome (CIS) patients, but predicted Expanded Disability Status Scale (EDSS) progression. Significance, however, was dependent on covariates, and confirmation in an independent study was required.<sup>3</sup>

The aim of this study was to test if the gMS-Classifier1 could predict early disability progression in a large multicenter cohort of patients with CIS or relapse-onset MS.

Blood samples and clinical data were prospectively collected in four MS centers between 1993 and 2007: The Ottawa Hospital, Ottawa, Canada; Amsterdam University Medical Centers, the Netherlands; UMass Memorial Medical Center, Worcester, USA; and Hospital Ramón y Cajal, Madrid, Spain. Patients had a diagnosis of CIS ( $n=118$ ) or relapsing remitting multiple sclerosis (RRMS;  $n=240$ ) at study onset. Age at blood sampling was between 18 and 50 years. Serum samples were stored frozen  $<-70^{\circ}\text{C}$  until assayed.

Baseline (EDSS) was performed within 6 months of blood sampling and was repeated during patient routine visits. Disability progression was defined as a sustained ( $\geq 6$  months) progression of at least 1.0 EDSS point over the baseline EDSS and progression to an EDSS score of 3.0 or higher.

Mean follow-up was 94 months.

In 2012, frozen serum samples were shipped to Glycominds Inc Lab (Simi Valley, CA, USA) for testing for anti-glycan antibodies as described before.<sup>3</sup> If

one of the antibodies was above the predefined cut-off (anti-GAGA2  $>148.8$  EIA units, anti-GAGA3  $>164.6$  EIA units, anti-GAGA4  $>133.6$  EIA units, and anti-GAGA6  $>168.1$  EIA units), patients were considered positive for the gMS-Classifier1. There were no significant differences for the key variables gMS-Classifier1 and EDSS progression between the four centers.

Of the 358 patients, 44 (12.3%) were gMS-Classifier1 status positive. EDSS progression was available for 355 patients, of whom 158 (44.5%) had confirmed progression at the end of follow-up. The percentage of patients showing EDSS progression did not differ between the groups, using the 1 point EDSS progression definition ( $p=0.587$ ) or for EDSS progression above 3.0 ( $p=0.771$ ). There was no association between EDSS progression and the gMS-Classifier1 ( $p=0.778$ ) or positive titres for any of the separate antibodies (anti-GAGA2:  $p=0.934$ , anti-GAGA3:  $p=0.663$ , anti-GAGA4:  $p=0.712$ , and anti-GAGA6:  $p=0.440$ ).

No statistical differences between the gMS-Classifier1 positive and negative group were observed for age ( $p=0.631$ ), disease duration ( $p=0.147$ ), gender ( $p=0.154$ ), baseline EDSS ( $p=1.000$ ), number of CIS patients at blood sampling ( $p=0.865$ ), follow-up time ( $p=0.587$ ), relapse at blood sampling ( $p=0.771$ ), and steroids at blood sampling ( $p=1.000$ ).

Here, we present the results of a large cohort of patients from different centers from two continents, showing no statistical differences between gMS-Classifier1 positive and negative patients, convincingly indicating that the gMS-Classifier1 does not predict disability progression in MS.

**Declaration of Conflicting Interests**

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## Analysis of Canadian multiple sclerosis patients does not support a role for FKBP6 in disease

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We read with interest a recent article by Mescheriakova et al.<sup>1</sup> entitled *Linkage analysis and whole exome sequencing identify a novel candidate gene in a Dutch multiple sclerosis family*. In this study, the

authors described a missense variant in *FKBP6* (p.R183C, rs147213094) co-segregating with multiple sclerosis (MS) in eight individuals from a large Dutch multi-incident family. Four healthy family members were also found to harbour this mutation, and it was not observed in one family member diagnosed with MS. Reduced penetrance and the presence of phenocopies does not detract from the authors' claim as familial forms of complex diseases, including MS, frequently are genetically heterogeneous.<sup>2–5</sup> In addition, albeit not statistically significant,

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