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Genetic variants associated with intrathecal synthesis of IgG, IgM and IgA in multiple sclerosis

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Introduction: Intrathecal synthesis of immunoglobulins can often be observed in patients with multiple sclerosis (MS) and clinically isolated syndrome (CIS) and the amount of intrathecal immunoglobulin synthesis in an individual patient remains relatively stable over time. We could previously show an association between the IgG index and genetic variants located around the immunoglobulin heavy chain locus (IGHC) on chromosome 14 using a genome wide association study (GWAS). The variants corresponded to different allotypes that code for structurally distinct immunoglobulin heavy chains. The aim of this study was to confirm the previously described association by genotyping the single nucleotide polymorphism (SNP) rs74093865, which is in strong linkage disequilibrium (r^2 0.9) with the lead SNP rs10136766 from our previous study and to further investigate the effect of this genetic variant on intrathecal synthesis of IgA and IgM.

Methods: DNA samples from 785 MS or CIS patients with available data on intrathecal immunoglobulin synthesis, who were not part of our previous study, were obtained and genotyped for the rs74093865 using a TaqMan SNP genotyping assay . The association between rs74093865 and rank transformed IgG, IgM and IgA indices was tested using linear regression with adjustments made for sex, age, assay plate, time points of lumbar puncture and DNA sampling.

Results: rs74093865 was significantly associated with indices for IgG, IgM and IgA in patients with MS and CIS. In accordance

with our previous findings, the A allele, which corresponds to the IGHC Gm21* allotype, correlated with higher IgG index (p=2E-13). Interestingly, lower IgM and IgA indices were seen in patients carrying the A allele of rs74093865 (p=3E-7 and p=5E-4 for IgM and IgA indices, respectively).

Conclusion: The results of this study confirm the association of a genetic variant located around the immunoglobulin heavy chain locus with intrathecal immunoglobulin synthesis. Interestingly the Gm21* allotype seems to be associated with higher intrathecal IgG synthesis and lower intrathecal IgA and IgM synthesis.

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