Karolinska Institutet

Institutionen för klinisk neurovetenskap

Common Viruses and Host Gene Interactions in Multiple Sclerosis

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska
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ABSTRACT

Multiple sclerosis (MS) is a neurological disorder, characterised by demyelination and inflammation of the central nervous system, leading to sensory and motor symptoms. MS is thought to be complex disease, with both environmental and genetic risk factors underlying disease susceptibility. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections are two environmental risk factors, one with a robust association to MS (EBV) and one where the results have been more inconclusive (CMV). The strongest genetic risk factors lies within the HLA genes, with *HLA-DRB1*15* as the strongest susceptibility factor, and *HLA-A*02*, as the most protective genetic factor.

In **paper I**, the role of EBV infection, and the interaction with *HLA-DRB1*15* and *HLA-A*02* was studied. Anti-EBNA1 IgG was measured, as was IgG antibodies towards 5 different epitopes of EBNA1. High levels of EBNA1 385-420 IgG antibodies were strongly associated with MS, independent of EBNA1 IgG antibody level. There was interaction on the additive scale between EBNA1 385-420 IgG and *HLA-DRB1*15* and absence of *HLA-A*02.* In **paper II**, we tried to replicate findings by Simon et al, where they found interaction on the multiplicative scale between EBNA1 IgG levels and smoking (never/ever), but our analysis showed no such interaction.

In **paper III**, the association between CMV and MS was studied, yielding a significant negative association between CMV and MS. To further validate our results, a meta-analysis of published retrospective studies was performed, which provided a similar negative association, supporting our results.

In **paper IV**, the focus shifted from the association of viruses to MS, to dissecting the host genetic influence on anti-JCV seropositivity and anti-JCV antibody levels. JC virus is the virus responsible for Progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal side-effect seen in MS-patients treated with natalizumab. A meta-analysis of three genome wide association studies performed in two sets of MS cases, one Scandinavian and one German, and a set of Swedish controls, strongly indicated that the HLA class II region was involved in regulating anti-JCV antibody response, and anti-JCV antibody levels. Analysis of classically named HLA-alleles supported these findings. The alleles in the DRB1*15-DQB1*06:02-DQA1*01:02-haplotype were all strongly negatively associated with anti-JCV antibody status and low anti-JCV antibody levels. The alleles in the DRB1*13-DQB1*06:02-DQA1*01:03-haplotype were positively associated with anti-JCV antibody status. Several non-HLA loci were suggestively associated with anti-JCV antibody status and anti-JCV antibody levels (p<0.0001). However, these findings will have to be replicated in an independent dataset.

This thesis highlights the interactions between environmental and genetic factors in modulating MS risk. It also shows that the HLA genes have a central role in the susceptibility to JCV infection.