Institutionen för klinisk neurovetenskap

HLA genetics in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic disease in which both genetic and environmental risk factors contribute to disease susceptibility. MS patients suffer from inflammatory lesions in the central nervous system which results in demyelination of nerve cells, reduced neuronal activity and finally neurodegeneration. The immune system has a central role in MS pathogenesis and human leukocyte antigen (HLA) molecules are key players. The genes encoding HLA class I and II molecules are highly polymorphic isotypically and allotypically which makes it problematic to identify which variants affect disease susceptibility.

The strongest genetic risk factor for MS is a haplotype of HLA class II alleles, \textit{DRB1*15:01, DRB5*01:01, DQA1*01:02, DQB1*06:02} (below referred to as \textit{DRB1*15}) which increases the risk of MS 3-fold compared with the general Swedish population where the lifetime risk of MS is 0.2%. Our group pioneered the identification of a protective effect of the HLA class I region, by discovering that \textit{HLA-A*02} decreases the risk of MS by 40%. The main focus in this thesis has been to identify additional HLA factors, if any, that influence MS susceptibility.

In papers I and II we genotyped 1,784 Swedish and Norwegian MS patients and 1,660 controls, for \textit{HLA-DRB1, HLA-A, HLA-C}, and eventually also \textit{HLA-B}, and applied several statistical methods, mainly logistic regression analyses. We conclude that, in addition to the roles played by \textit{DRB1*15} and \textit{HLA-A*02}, additional influence on susceptibility is exerted by \textit{HLA-DRB1*01, HLA-DRB1*07} and \textit{HLA-B*12}, which are negatively associated with MS and \textit{HLA-B*14} which increases the risk of MS. Analysis based on haplotypes, rather than on alleles, showed that a haplotype carrying \textit{HLA-A*02, HLA-C*05} and \textit{HLA-B*12} is markedly protective, reducing the risk of MS 2.4-fold, also outweighing the risk of \textit{HLA-DRB1*15} when present on the same haplotype.

Paper III focuses on a possible interaction between genetic background (\textit{DRB1*15}) and an environmental influence, a month-of-birth effect on MS risk. We demonstrate that patients born in April have a higher risk of being \textit{DRB1*15} positive. On the contrary, patients born in November have a lower risk of being \textit{DRB1*15} positive. We hypothesize that pregnancies exposed to a lower degree of sunlight thus lower levels of Vitamin D, confer an increased risk for a \textit{DRB1*15} positive child to later develop MS.

In paper IV the influence of HLA genes on the risk of developing neutralizing antibodies (NAbs) to interferon beta (IFN-\beta) treatment was studied. We show that the risk allele for MS, \textit{HLA-DRB1*15}, is also a risk factor for development of NAbs in patients treated with high dose subcutaneously administered IFN-\beta 1-a, but not for IFN-\beta 1-b. \textit{DRB1*15} is also a risk factor for developing antibody titers high enough to abolish the effect of treatment. Thus, the genetic risk of NAbs varies with IFN-\beta formulation.

This thesis adds several pieces of information to the large MS genetics puzzle and suggests several roles of HLA genes and molecules that should be further investigated.

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