Using genome-wide association studies to better understand multiple sclerosis

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Abstract

Neurological diseases have a substantial and growing impact in our society. Multiple Sclerosis is one of the most common neurological disorders. Life-time risk of developing the disease is 1/500 in north-western Europe. Approximately 1.3 million individuals worldwide and 10,000 individuals in Belgium suffer from the disease. Onset of the disease typically occurs in early adulthood, between 20 and 40 years of age, at the start of building out a family and a professional career. The disease leads to significant physical and cognitive disability and hence has an important impact on the personal, social and professional life of patients and their relatives. The currently available treatments are only partially effective. The pathogenesis of the disease has not been unravelled yet, but the past years have seen exciting progress in the field. A large number of genetic risk factors have been identified, and patients differ in which combination of genetic risk factors they carry. We now are facing the challenge of translating this list of genes into an improved understanding of disease mechanisms and hopefully to better treatments.

Keywords: multiple sclerosis, genome wide association study, human genetics.
Multiple sclerosis (MS) is the most common chronic neurological disease among young adults. In Belgium more than 10,000 persons suffer from this disease. The first symptoms generally appear between 25 and 35 years of age. The disease therefore typically affects young adults and leads to physical as well as cognitive disability which frequently results into psychological and social problems.

MS is an autoimmune disease of the central nervous system, which is constituted by the brain and the spinal cord. MS is characterized by the presence of multiple plaques in the central nervous system consisting of inflammatory cells, demyelination and gliosis. The myelin destruction occurs by inflammatory cells, and influences nerve conduction. This inflammatory and demyelinating processes are together called the immune component of MS. In addition, axonal loss occurs early in the disease and largely contributes to the permanent neurological disability and disease progression. This is the degenerative component of MS. Both the immune and the degenerative component are constituted by cascades and networks, and also interact. At the clinical level both components translate differently. The immune component consists of bouts of inflammation, which are visible on the MRI scan by the appearance of new lesions, some of which cross the threshold of producing symptoms, which then constitute a relapse. The degenerative component starts early in the disease, but becomes clinically apparent at a later stage and is translated clinically as a progressive disease course. In some patients the immune component is clinically silent: we call this a primary progressive disease course (http://www.ncbi.nlm.nih.gov/pubmed/18970977). In the majority of the patients however, there is a relapsing-remitting disease course, evolving to secondary progressive MS.

The symptoms in MS range from visual disturbance over sensory problems, weakness, coordination and bladder problems to cognitive and psychiatric symptoms and fatigue. These symptoms vary from patient to patient, and within one patient from time to time. This leads to the typical clinical heterogeneity of this disease. Although MS often invokes the image of a wheelchair bound patient, other patients do not have any visible symptom and are able to lead a normal life, at least during a variable part of their disease course.

Over the last 15 years a lot of progress has been made regarding the treatment of MS. However, we have to admit that these treatments are only partially effective, and that these only address the immune component of the disease, which is clinically translated to as relapses. These drugs do not affect the neurodegenerative component of MS, and therefore do not influence the progressive course of the disease, as we see in primary or secondary progressive MS.

Current treatment options consist of first and second line treatments which both affect relapse frequency. Interferon-beta and glatiramer acetate have been used as first line treatments for 15 years now. These are considered to be immunomodulatory drugs. They reduce the relapse frequency by 30% and are safe. However, interferon beta and glatiramer acetate need to be injected intramuscularly or subcutaneously and do have side effects, such as flu-like symptoms and injection site reactions. It has been shown that starting these drugs early in the disease course, not only reduces the relapse frequency, but also delays disability. Indeed, in the Benefit study patients were randomized into two groups: one received interferon-beta from the very first relapse, and the other from the second relapse. The early treated group experienced their second relapse 2 years later than the delayed treatment group. Also, when measuring disability with the EDSS score,
there was a slower increase of disability in the early treated patients.

More recently two new drugs became available. Tysabri is a monoclonal antibody against an adhesion molecule on lymphocytes and monocytes. It interferes with the adhesion of lymphocytes to the endothelium and reduces the passage of these inflammatory cells through the blood-brain barrier. This results in a reduction of new lesion formation in the central nervous system.

Tysabri is highly efficacious, with a relapse frequency reduction of 68%. As anticipated from this effect on relapses, there is also a clear effect on the accumulation of disability. Tysabri is administered by monthly infusions and is generally well tolerated. Unfortunately, it may lead to the development of progressive multifocal leukoencephalopathy, a very severe and sometimes fatal viral infection of the brain by the JC Virus, and therefore is only available as a second line treatment.

The most recent new drug on the market is Gilenya, which is an S1P receptor inhibitor leading to the retention of lymphocytes in the lymph nodes. It also downregulates some inflammatory genes, and has a direct effect on astrocytes and therefore would have some neuroprotective properties.

Gilenya has shown a relapse frequency reduction by 55% in relapsing-remitting MS, and also delays the accumulation of disability. It is the first oral drug in MS. The most frequent side effects are transient bradycardia during the first dose, which requires monitoring in the hospital for 6 hours, reversible macular edema, and an increase of blood pressure and of infections of the lower respiratory tract. Safety on the long term still needs to be evaluated, and in the meantime Gilenya is available as a second line treatment in Europe as well.

There are several other drugs in development, which all interfere with various steps in the pathogenesis of the disease. Some of them have already shown encouraging results, and we are expecting them on the market during the coming years. The challenge for the neurologist will therefore be to decide which drug to prescribe to which patient. Efficacy needs to be outweighted against risks and side effects, and we would welcome biomarkers which help us to individualize treatment choices based on expected efficacy or side effects in a particular patient. To develop such biomarkers it may be helpful to better understand the disease.

The exact etiology of MS is of course unknown, but we know about several factors that influence or may influence the susceptibility for the disease. Since MS occurs more frequently in women, relapse frequency is lower during pregnancy but higher during the postpartum period, hormonal factors may play a role. It is also known that environmental factors are involved, which is clear from the dependence of the MS prevalence on the latitude. Relapses may be triggered by infectious agents, and there is still debate about a possible contribution of stress and trauma.

There is also an important role of genes in the susceptibility to MS, which is clear from the recurrence risks in related persons. The lifetime risk to develop MS in a person without family history is 0.2%. This increases if there is another family member with MS and the recurrence risk increases when the genetic sharing increases, e.g. 4% in siblings, 15% in siblings with one affected parent, 25% if both parents are affected, and 30% in monozygotic twins.

Since 1972 it is known that this risk is associated with HLA: the relative risk to develop MS is three times higher when carrying the HLA-DRB1*1501 variant on chromosome 6. However, carrying the HLA-DRB1*1501 variant is not a prerequisite for developing MS. Indeed, 24% of the general Belgian population is carrying at least one HLA-DRB1*1501 allele and does not develop MS. Also, 48% of MS patients in Belgium do not carry this
allele and still have the disease \(^3\) (http://www.ncbi.nlm.nih.gov/pubmed/18647361).

Between 1972 and 2007 a lot of efforts have been done to determine other genetic risk factors, but results were never replicated. These disappointing results led to international collaborations through which patient numbers could be raised.

Together with technologic evolutions and the knowledge of the human genome this resulted in the discovery of 26 new risk genes in 2007\(^4\). This resulted in further collaboration of researchers in Europe and the US, and the Welcome Trust. They joined forces in the International MS Genetics Consortium in 2009, which led to a sample size of nearly 10,000 MS patients and more than 17,000 controls. The study population consisted of samples from Europe, US, Australia and New-Zealand. Belgium was represented by contributing samples of 544 MS patients.

Results from this genome-wide association study\(^5\) (figure 1) first of all confirmed the role of the HLA-DRB1*1501 variant, but also showed involvement of 4 other HLA alleles. It is important to note that the odds ratio’s for these alleles vary from 0.73 to 2.40 end thus are significantly lower than that for the HLA-DRB1*1501 variant, for which the odd’s ratio is 3.10. This means that each variant has a small effect on disease susceptibility, which explains why these results were only found in these large study populations.

Regarding the non-HLA susceptibility loci the study confirmed 23 of the 26 in 2007 reported loci. Additionally 34 novel loci were found, which brings the number of susceptibility loci now at 57. It is important to note again that the odds ratios are low, meaning that the effect of each region of association is low. Also these variants occur in the general population, not only in patients with MS.

These susceptibility loci are located in the neighbourhood of several genes, and in order to learn more about the mechanism whereby a variant influences disease susceptibility it is important to look at the function of these genes. It was found that mainly the pathways that are involved in the immune system are enriched: 19 from the 57 hits (30%) are involved in the immune system, whereas this is only 7% in the general population. Immune functions in which those genes interfere are antigen presentation and T helper cell differentiation.

Two other observations are interesting from this study. First, 30% of the identified regions overlap with other autoimmune diseases, which may give some clues about autoimmunity in general. Secondly, it appears that 2 of the identified genes are already a target of existing therapies. Indeed, daclizumab targets the IL2 receptor, and Tysabri the vascular adhesion molecule. These 2 genes were identified as risk genes for developing MS.

Apart from disease susceptibility, it is important to see if the clinical heterogeneity could be explained from these genetic findings. First, the study confirms the role of HLA-DRB1*1501 in the age at onset of the disease: for each copy of HLA-DRB1*1501 the risk to develop MS at a younger age increases. For disease course however, no genetic basis was found, which means that if one patient develops primary progressive MS, and the other one relapsing remitting MS this is not driven by genetic differences. Finally, disease severity as measured by the MSSS, which takes into account the time needed to reach a certain EDSS, is also independent from the genetic characteristics. We thus conclude that the latest GWAS resulted in 57 susceptibility loci for MS, of which 34 are new, and confirmed the role of HLA-DRB1*1501 in the age of onset of disease. It is now of course possible to look at correlation between the genetic profile and other clinical or paraclinical markers, such as MRI or CSF findings.
Figure 1 (from Nature 2011): Regions of the genome showing association to multiple sclerosis. Columns from left to right: evidence for association from the linear mixed model analysis of the discovery data (thresholded at −log10(p) = 12). Non-MHC regions containing associated SNPs are shown in red and are labelled with the rsID (bold for newly identified loci, black for strong evidence, grey for previously reported) and risk allele of the most significant SNP. * indicates that the locus contains a secondary SNP signal. Odds ratio and 95% confidence intervals estimated from the meta-analysis of the discovery and replication data (+ indicates estimates for previously-known loci from discovery data only). Risk allele frequency estimates in each of the control populations used in the study (each is shown as a vertical bar on a scale from 0 to 1 going left to right). For each region of association the number of genes is reported, and where non-zero a candidate gene is given. Black dots indicate that the candidate gene is physically the nearest gene included in the “immune system process” GO term. When the most-significant SNP tags a SNP predicted to have an impact on the function of the candidate gene this is indicated. Where such a SNP exists, the gene involved is selected as the candidate gene; otherwise the nearest gene is selected unless there are strong biological reasons for a different choice. The final column indicates SNPs which are correlated (r² > 0.1) with SNPs reported to be associated with other autoimmune (AI) diseases (abbreviations: RA = Rheumatoid arthritis; CeD = Celiac disease; UC = Ulcerative colitis; CrD = Crohn’s disease; T1D = Type 1 diabetes; PS = Psoriasis).
In conclusion, the results of this latest genome wide association study in MS do not allow us to predict who will develop MS and who will not since the effect of each variant on susceptibility is small, and there is overlap in genetic variants between patients and controls. However, the importance of the study lays in the identification of pathways that play a role in MS development. The study of the exact function of the identified genes is only starting now, and it is anticipated that this will lead to new, better and safer treatments. Finally, it is hoped that correlations between this genetic information and clinical or paraclinical information will help the neurologist to personalize treatment.
LIST OF REFERENCES


