HAS GENETICS ADVANCED OUR UNDERSTANDING OF MULTIPLE SCLEROSIS (MS)?

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It was recognised in the late 19th century that some people with multiple sclerosis have an affected relative. But not until the mid-1980s was it finally established, based on recurrence risks in many categories of relatives of index cases, that disease susceptibility is genetically determined. By then, it was already clear that northern Europeans have a high frequency of multiple sclerosis whereas the disease in much less common in Asians, Orientals and Africans. In the 1970s, dissection of the class II human major histocompatability complex (MHC) revealed the DR15 and related associations. This early success based on small numbers of cases and controls led to some complacency that the rest of the genetic story would easily unfold but this did not prove to be the case. The period 1989-1999 was marked by uncertainty on which strategy should be used to unravel the complex genetics of multiple sclerosis. In the early 1990s, tools emerging from the human genome project allowed systematic genome screening to be performed. Although influential in refining concepts on the genetics of multiple sclerosis, these studies were under-powered. The first substantial screen for linkage, in 2005, found no markers other than those encoded in the MHC with genome wide significance. A summary of the headlines to 2007 might read:

- Multiple sclerosis is familial (Hermann Eichorst, 1896); and the disease shows racial susceptibility and protection (Charles Davenport, 1921)
- Multiple sclerosis is associated with the histocompatibility antigen HLA-A3 (Caspar Jersild and Arne Svejgaard, 1972) and HLA-Dw2 (Paul Terasaki and others, 1976)
- First molecular studies of susceptibility factors in multiple sclerosis (Daniel Cohen, 1984)
- Updated twin and other family studies (George Ebers, 1986 and others)
- First whole genome linkage screens (Stephen Sawcer, George Ebers, and Steve Hauser, 1996)
- First whole genome association screen (Stephen Sawcer and the GAMES consortium, 2002)
- First whole genome high density linkage screen (Stephen Sawcer and the International Multiple Sclerosis Genetics Consortium, 2005)
- First semi-high resolution whole genome association screen (Daniel Cohen and Serono, 2005 unpublished)
- First high resolution whole genome association screen (International Multiple Sclerosis Genetics Consortium, 2007)

Starting in 2007, adequately powered studies indicated that the MHC class I gene *HLA-C* exerts an independent effect on susceptibility confirming previous research suggesting complexity and allelic heterogeneity in the MHC. And in the same year, evidence gathered from a number of sources identified *IL7Rα* as a further susceptibility locus in multiple sclerosis. This result emerged from the application of genomic convergence, in which information from several published sources was used to identify a short list of candidate genes; subsequent investigation of SNPs from these genes revealed association with the single nucleotide polymorphism (SNP) rs6897932 from the *IL7Rα* gene. Formation of the International Multiple Sclerosis Genetics Consortium (IMSGC) in 2003 provided an up-lift in collaboration coinciding with progress in the human genome project so that the stage was reached whereby systematic screening for association became possible. The IMSGC, typed 334923 SNPs in 931 trio families using the Affymetrx 500k genotyping chip: in a second screen, performed as part of the Wellcome Trust Case Control Consortium, 12374 non-synonymous SNPs (nsSNPs) were typed in 975 cases and 1466 controls (from the 1958 birth cohort) using the Illumina Infinium system. These screens, involved 1.5 billion and 38.6 million genotypes respectively. Amongst the prioritised markers SNPs coding for *IL7Rα,* and *IL2Rα* and a protein kinase involved in ciliary neurotrophic factor signalling (*TYK2*) were identified.

Subsequent replications in increasingly large cohorts of cases derived from European, north American and Australian populations of Caucasians compared with local and generic controls have added *cd226* (DNAM1) and *CLEC16A* to the list of genes that show association with multiple sclerosis at or above levels of significance needed to demonstrate positive results in studies involving many independent genotypes. Taken together, in 2008, the convergence of results across these screens makes it possible to list seven genetic loci that appear to confer susceptibility to multiple sclerosis: these are HLA-DRB1 ($p=8.9\times10^{-81}$), HLA-C ($p=3.3\times10^{-5}$), c*d25* (IL2-Rα: $p=9.6\times10^{-29}$), *IL7R* (IL7-Rα: $p=5.5\times10^{-20}$), *TYK2* (Tyk2: $p=2.7\times10^{-6}$), *cd226* (DNAM1: $p=5.4\times10^{-8}$) and *CLEC16A*($p=1.6\times10^{-15}$). The relative risk for each is small indicating that, alone, these genes make a small contribution to susceptibility. Their epistatic effects and the extent to which amplification of the effects is conferred on defined pathways remains to be determined. But the on-going deployment of this large resource of well validated cases and the availability of generic controls will continue to identify additional genes that influence susceptibility to multiple sclerosis at equally impressive levels of statistical significance.

Against this background it might seem redundant to debate whether genetics has advanced our understanding of multiple sclerosis. If all research in multiple sclerosis is motivated by the need to understand disease mechanisms and derive safe and effective treatments, the revelation that all seven of the genes now shown to confer susceptibility are involved in regulation or effector pathways of the immune response provides a vital clue to the nature of the dominant disease mechanism in this disease; and since the cases studied are not stratified for phenotype or other laboratory biomarkers, these data add weight to the analysis that, although different effector mechanisms may be involved, the disease is complex but not heterogenous and driven by the core process of focal brain inflammation. To this analysis can be added evidence from the clinical trials, themselves subtended by dedicated research into the aetiology and pathogenesis, for significant modification of the clinical course through effective immunosuppression early in the course of active relapsing-remitting multiple sclerosis.