HAS GENETICS ADVANCED OUR UNDERSTANDING OF MULTIPLE SCLEROSIS (MS)? ASK NOT WHAT MS CAN DO FOR GENETICS BUT WHAT GENETICS CAN DO FOR MS

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Multiple sclerosis (MS) is a syndrome defined clinically by neurological symptoms and signs together with MRI findings supportive of inflammatory demyelinating lesions. The inherent limitations of studying a syndrome rather than a disease mean that we do know the etiology and pathogenesis of MS and can therefore offer only limited therapy without a definite cure. The great hope has been that genetic data generated through linkage analysis would provide causative genes in MS that would provide subgroups of patients with well defined diseases. A MeSH based search of the Pubmed database for MS/genetics found 2329 papers the first of which is from 1957 on the subject of twin studies in MS. In spite of exponentially growing body of data, more than 50 years of research has not yet made the significant advances as have been made in other major neurological syndromes such as dementia, movement disorders, epilepsy and peripheral neuropathy. An enormous effort has been put into genetic studies since MS seems to be a multi-factorial genetically determined disease the genetic unraveling of which should potentially shed light on other similar diseases.

Those genes that have been found are almost exclusively linked to functions of the immune system. Though important by itself, this is hardly new information in a disease that has been considered to be inflammatory for the last 100 years. The linkage to the HLA region has been confirmed beyond any doubt but the implications for the pathogenesis of MS is still unclear. White matter degenerative diseases such as adrenoleukodystrophy (ALD) are potential causes of MS. There is, however, no clear support for genes involved in degenerative white matter diseases. There are studies on disease severity genes, APOE for example, but most of these genes are probably not specific for MS and have not contributed yet to therapy.

Though there has been an interest in new pathways such as coagulation, these have been generated mainly by protein expression analysis and functional studies.

Animal studies offer great potential to pick up significant genetic factors. Certain strains of mice develop the experimental autoimmune encephalomyelitis model MS while most do not. There is also a specific interaction between the type of immunogen used and the strain that responds with overt disease.

One significant way forward would be to improve the diagnosis of MS by sub-classifying it into more specific syndromes. A striking example of such a process has been the reclassification of patients with neuromyelitis optica (Devic).

Finally, an enormous effort has been invested in the genetics of MS with limited significant advances to date. Hopefully the larger data sets and advanced methods of analysis now available will bring the long awaited major breakthroughs.