Causes of Multiple Sclerosis: a functional genomics approach

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Multiple Sclerosis (MS) is the most common disabling neurological disease affecting young adults in Western Society. To date, 55 strongly associated single nucleotide polymorphisms have been discovered. We now need to identify causal genes. While T-cells as targets for therapeutic intervention have rarely proven useful, there is strong clinical and in-vitro data identifying NK cell deficiencies in patients, and key roles for monocytes in myelin and axon destruction and autoantigen presentation. RNA extracted from magnetic bead sorted monocytes and NK cells, of healthy controls (HC) and untreated patients with relapsing remitting MS (RRMS), was labelled and hybridised to Affymetrix Human Gene 1.0 ST arrays. Expression values were standardized across chips using RMA and quantile normalization as implemented in GenePattern. Genes were ranked by expression difference significance by Mann Whitney U test and ANOVA. To date, we have analysed monocytes of 30 patients and 39 HC, and NK cells from 25 patients and 32 HC. Expression differences of those genes adjacent to MS associated risk SNPs lying between 110kb upstream and 40kb downstream of a candidate gene were considered. We have identified three genes worthy of further analysis on this basis: RGS1, HHEX and THEMIS. To test the relevance of these candidates to central nervous system (CNS) autoimmunity, we aim to mimic phenotypes associated with these expression quantitative trait loci (eQTL) in in-vitro cultures of purified NK cells and monocytes, and in-vivo in a mouse model of MS - experimental autoimmune encephalomyelitis (EAE).