Interplay between genes reveals more about the risk of MS

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The International MS Genetics Consortium, which includes Australian and New Zealand researchers via the MS Research Australia-supported ANZgene collaboration, has revealed further details of how genes interact to determine an individual's risk of developing MS.

The results were published in the prestigious journal *Nature Genetics*.

The Consortium had previously revealed over 100 individual changes to genes that increase, or decrease, a person's susceptibility to MS. Now using their extensive collection of DNA samples from over 17,000 people with MS and 30,000 healthy control individuals, the group have analysed how the genes might work together to determine the risk of developing MS.

There are two particular groups of genes that have the strongest influence on genetic risk of MS. These are the family of immune system genes known as HLA class I and HLA class II.

Previous research has shown that variations in the HLA class II genes, in particular the HLA-DRB1*15:01 gene, substantially increase the risk of MS. Variations in the HLA class I genes on the other hand, are largely protective against MS. It is also know that generally, the risk from single HLA genes can be 'added together' to determine the overall risk of developing MS in a person – the more risk genes present in an individual the higher their risk of MS.

This study confirmed these findings, but further investigated how the genetic changes in the HLA gene family might work together to determine individual risk. The study showed some pairs of genes worked together to modify the risk of MS – for example one of the HLA class I genes is protective against developing MS but this is only seen in people who also have the main risk gene HLA-DRB1*15:01. In another pairing, the presence of the HLADQB1*03:01 gene abolished the increased risk caused by the HLADQB1*03:02 gene.

Another major question is whether the HLA family of genes interact with the other 98 genes known to affect a person's risk of MS. These genes are also primarily genes related to the immune system, but the researchers found that these genes did not influence or change the risk conferred by the HLA family of genes.

Overall this analysis suggests a relatively straight forward picture of protective and risk HLA genes in MS which act relatively independently of the other risk genes, which differs from the situation seen in some other inflammatory diseases.

The relative lack of specific interactions between the HLA class I and class II genes also suggests that the two groups of genes act via different mechanisms in immune cells, raising the exciting possibility that it might be possible to manipulate or mimic the effect of protective genes as a means to treat MS.

Much more work is needed to understand the effects of the different genes involved in MS and reveal more about how they change the function of immune cells to contribute to MS disease biology. But these findings are an important step in untangling the complex role that genes and environmental factors play in causing MS.