MedicalXpress

Genetic study shows direct link between vitamin D and MS susceptibility 'gene'

February 5 2009

Researchers have found evidence that a direct interaction between vitamin D and a common genetic variant alters the risk of developing multiple sclerosis (MS). The research, published on 6 February in the open-access journal *PLoS Genetics*, suggests that vitamin D deficiency during pregnancy and the early years may increase the risk of the offspring developing MS later in life.

MS is the most common disabling neurological condition affecting young adults. More than 85,000 people in the UK and 2.5 million worldwide are thought to suffer from the condition, which results from the loss of nerve fibres and their protective myelin sheath in the brain and spinal cord, causing neurological damage.

The causes of MS are unclear, but it has become evident that both environmental and genetic factors play a role. Previous studies have shown that populations from Northern Europe have increased MS risk if they live in areas receiving less sunshine. This supports a direct link between deficiency in vitamin D, which is produced in the body through the action of sunlight, and increased risk of developing the disease.

The largest genetic effect by far comes from the region on chromosome six containing the gene variant known as *DRB1*1501* and from adjacent DNA sequences. Whilst one in 1,000 people in the UK are likely to develop MS, this number rises to around one in 300 amongst those carrying a single copy of the variant and one in 100 of those carrying two copies.

Now, in a study funded by the UK's MS Society, the MS Society of Canada, the Wellcome Trust and the Medical Research Council, researchers at the University of Oxford and the University of British Columbia have established a direct relationship between *DRB1*1501* and vitamin D.

The researchers found that proteins activated by vitamin D in the body bind to a particular DNA sequence lying next to the *DRB1*1501* variant, in effect switching the gene on.

"In people with the *DRB1* variant associated with MS, it seems that vitamin D may play a critical role," says co-author Dr Julian Knight. "If too little of the vitamin is available, the gene may not function properly."

"We have known for a long time that genes and environment determine MS risk," says Professor George Ebers, University of Oxford. "Here we show that the main environmental risk candidate - vitamin D - and the main gene region are directly linked and interact."

Professor Ebers and colleagues believe that vitamin D deficiency in mothers or even in a previous generation may lead to altered expression of *DRB1*1501* in offspring.

The finding - that the environment interacts directly with the background genetics of MS - complements research recently published in *Human Molecular Genetics* by Professor Ebers's group. There, they showed that environment changes to the same gene region can increase the risk of developing MS even further and can be inherited. These so-called "epigenetic effects" are being seen as increasingly important by scientists and there may be ways in which the effects reported in these two papers are related.

"Epigenetics will have important implications, not only for MS, but for

other common diseases," says Professor Ebers. "For mothers, taking care of their health during their reproductive years may have beneficial effects on the health of their future children or even grandchildren."

The authors hypothesise that this gene-environment interaction may affect the ability of the thymus, a key component of the immune system, to perform its regular tasks. The thymus produces an army of T cells, which identify invading pathogens, such as bacteria and viruses, and attack and destroy them. There are millions of different T cells, each designed to recognise a specific pathogen, but there is a risk that one type might mistakenly identify one of the body's own cells or proteins.

Ordinarily, the thymus will regulate the T cells and delete those that pose the greatest risk of attacking the body's own cells and proteins. However, the researchers believe that in people who carry the variant, a lack of vitamin D during early life might impair the ability of the thymus to delete these T cells, which then go on to attack the body, leading to a loss of myelin on the nerve fibres.

"Our study implies that taking vitamin D supplements during pregnancy and the early years may reduce the risk of a child developing MS in later life," says lead author Dr Sreeram Ramagopalan. "Vitamin D is a safe and relatively cheap supplement with substantial potential health benefits. There is accumulating evidence that it can reduce the risk of developing cancer and offer protection from other autoimmune diseases."

The research has been welcomed by Simon Gillespie, Chief Executive of the MS Society (UK).

"These remarkable results tie together leading theories about the environment, genes and MS but they are only part of the jigsaw," says Mr Gillespie. "This discovery opens up new avenues of MS research and

future experiments will help put the pieces together."

Citation: Ramagopalan SV, Maugeri NJ, Handunnetthi L, Lincoln MR, Orton S-M, et al. (2009) Expression of the Multiple Sclerosis-Associated MHC Class II Allele HLA-DRB1*1501 Is Regulated by Vitamin D. PLoS Genet 5(2): e1000369. doi:10.1371/journal.pgen.1000369, www.plosgenetics.org/article/i … journal.pgen.1000369

Source: Public Library of Science