Rare gene variant implicates vitamin D in multiple sclerosis

**8 December 2011**

A rare genetic variant that appears to be directly and causally linked to multiple sclerosis (MS) has been identified by Oxford University researchers.

Importantly, the mutation in the CYP27B1 gene affects a key enzyme which leads people with the variant to have lower levels of vitamin D, adding weight to the suggested link between vitamin D and MS.

The study was funded by the MS Society and is published in the journal Annals of Neurology.

The Oxford researchers, along with Canadian colleagues at the University of Ottawa, University of British Columbia and McGill University, set out to look for rare genetic changes that could explain strong clustering of MS cases in some families within an existing Canadian cohort study.

They sequenced all the gene-coding regions in the genomes of 43 individuals selected from families with four or more members with MS.

The team compared the DNA changes they found against existing databases, and identified a change in the gene CYP27B1 as being of interest.

The researchers then looked for the rare gene variant in over 3,000 families of unaffected parents with a child with MS.

They found 35 parents who carried one copy of this variant along with one normal copy.

In every one of these 35 cases, the child with MS had inherited the mutated version of the gene.

The likelihood of this gene’s transmission being unconnected to the MS is billions to one against, the researchers say.

The very strong implication is that in these particular cases of MS, low vitamin D levels are directly connected to the disease.

‘If inheriting the CYP27B1 gene variant was unrelated to MS, there would be a 50/50 chance of the child inheriting the variant from their parent,’ explains Professor George Ebers of the Nuffield Department of Clinical Neurosciences at Oxford University, who led the study.

‘All 35 children inheriting the variant is like flipping a coin 35 times and getting 35 heads, entailing odds of 32 billion to 1 against.

‘The odds are very much less probable than being hit by lightning,’ he says.

‘Is this gene variant causative in multiple sclerosis?

Pretty much!

The cornerstone for causation has always been the strength of association.

’Professor Ebers adds: ‘This type of finding has not been seen in any complex disease.

The uniform transmission of a variant to offspring with multiple sclerosis is without precedent but there will have been interaction with other factors,’ he adds.

Since the unaffected parent did not have multiple sclerosis, having a copy of this rare variant doesn’t mean someone will definitely develop the condition.

The researchers carried out a further test.

On the very rare occasions when people inherit two copies of the CYP27B1 gene variant, they develop a genetic form of rickets (a disease caused by vitamin D deficiency).

Norwegian collaborators found three such cases in the whole of Norway, and the researchers found that these three people all had MS as well.

The background incidence of MS in Norway is around 1 case in 1000 people.

Again, if the two conditions were unrelated, there would be a one in a billion chance of all three people with genetic rickets having MS as well.

Instead it suggests that CYP27B1 and MS are strongly associated.

The researchers believe there are wider implications of this finding.

They suggest that low levels of vitamin D are likely to play a role in MS more generally.

Studies across large populations have suggested a role for vitamin D in MS, but levels of the vitamin vary greatly between individuals according to their lifestyles, time out in the sun and diets.

There is good evidence that levels early in life are important, but it has not been easy to determine retrospectively years later what those levels might have been.

Therefore it has been difficult to conclusively draw a link.

The researchers explain that their study is an advance because they have essentially found a small group of people genetically determined to have vitamin D deficiency from birth and connected this directly to MS.

The Oxford team led by Professor Ebers now believe that a role for low levels of vitamin D in MS is now ‘broadly unequivocal’, as this new evidence adds to previous observational studies that have suggested sunshine levels (the body needs sunshine to generate vitamin D) around the globe are linked to MS and gene studies which have indicated vitamin D is involved in the regulation in key genes associated with the disease.

‘Large-scale studies of vitamin D supplements for preventing multiple sclerosis are now strongly warranted. The evidence is strong enough,’ says Professor Ebers.

‘It would be important particularly in countries like Scotland and the rest of the UK where sunshine levels are low for large parts of the year.

Scotland has the greatest incidence of multiple sclerosis of any country in the world.’

Dr Doug Brown, Head of Biomedical Research at the MS Society, said: ‘This is an important development and shines more light on the potential role of vitamin D deficiency on increasing the risk of developing MS.

This research is gathering momentum and will be the subject of discussion at an International Expert meeting in the USA this month; the outcomes of which will shape future research that will give us the answers we so desperately need about the potential risks and benefit of vitamin D supplementation.

’For more information please contact Professor George Ebers on +44 (0)1865 231903, +44 (0)7747 061843 or [george.ebers@ndcn.ox.ac.uk](mailto:george.ebers@ndcn.ox.ac.uk)  
Or the University of Oxford press office on +44 (0)1865 280530 or[press.office@admin.ox.ac.uk](mailto:press.office@admin.ox.ac.uk%20)

**Notes for editors**

* As a comparison for the size of these odds, the annual risk of death from lightning is just 1 in 18.7 million. The chances of winning the UK lottery are 14 million to 1. There are a list of risks, including the annual risk of dying from a lightning strike, on the Health and Safety Executive website on a page called ‘Risk education statistics’: <http://www.hse.gov.uk/education/statistics.htm#death>
* An accepted manuscript for the paper ‘Rare variants in the CYP27B1 gene associated with multiple sclerosis’ by Sreeram Ramagopalan and colleagues has been published online in the journal Annals of Neurology <http://onlinelibrary.wiley.com/doi/10.1002/ana.22678/abstract>
* The study was funded by the MS Society in the UK.\* Oxford University’s Medical Sciences Division is recognized internationally for its outstanding research and teaching, attracting the brightest minds from all over the world.  
    
  It is one of the largest biomedical research centres in Europe, with over 2,500 people involved in research and more than 2,800 students, and brings in around two-thirds of Oxford University’s external research income. Listed by itself, that would make it the fifth largest university in the UK in terms of research grants and contracts.  
    
  Oxford is home to the UK’s top-ranked medical school, and partnerships with the local NHS Trusts enable patients to benefit from the close links between medical research and healthcare delivery.  
    
  14 winners of the Nobel Prize for Physiology or Medicine worked or were educated at Oxford, and the division is home to 29 Fellows of the Royal Society and 68 Fellows of the Academy of Medical Sciences.  
    
  The development of penicillin at Oxford ushered in the modern age of antibiotics, and the confirmation of the link between smoking and cancer has prevented many millions of deaths. Oxford continues to be at the forefront of medical research, whether it’s the genetic and molecular basis of disease, the latest advances in neuroscience, or clinical studies in cancer, diabetes, heart disease and stroke. Oxford has one of the largest clinical trial portfolios in the UK and great expertise in taking discoveries from the lab into the clinic.  
    
  A great strength of Oxford medicine is its long-standing network of clinical research units in Asia and Africa, enabling world-leading research on the most pressing global health challenges such as malaria, TB, HIV/AIDS and flu. Oxford is also renowned for its large-scale studies which examine the role of factors such as smoking, alcohol and diet on cancer, heart disease and other conditions.