Rare gene variant implicates vitamin D in cause of multiple sclerosis

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The body gets most of its vitamin D from sunshine

(Medical Xpress) -- 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 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 one 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 one 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."

Provided by Oxford University