Nature Reviews Neurology **10**, 672 (2014); published online 4 November 2014; doi:10.1038/nrneurol.2014.210

MULTIPLE SCLEROSIS

Effects of IFN-β treatment on vitamin D levels in multiple sclerosis are modified by genetic variants

Genetic variants influence how treatment with IFN-β affects blood levels of vitamin D in patients with multiple sclerosis (MS), a new study reveals. The finding offers insight into the mechanism by which IFN-β reduces relapse rate in MS.

In 2012, a prospective cohort study at the University of Tasmania showed that IFN-β treatment increases blood levels of the vitamin D metabolite 25-hydroxyvitamin D (25[OH]D) in patients with MS, and that this effect is enhanced by exposure to the sun, indicating that IFN-β acts via the vitamin D pathway. The same research group, led by Bruce Taylor, has now analysed genetic data from the same cohort to examine the molecular basis of the effect.

"We hypothesized that there may be polymorphisms in vitamin D pathway-related genes that adversely affect vitamin D levels in patients with MS, and which IFN-β might be correcting," explains senior author Steve Simpson Jr. "Our thinking was that these genes would have variants that do not need correcting and, thus, there would be variability in the IFN-β–vitamin D association that would hint at which part of the pathway IFN-β acts on."

> "...randomized controlled trials involving vitamin D and/or IFN-β should take both factors into account..."

Using a cohort of 169 patients from the Southern Tasmanian Multiple Sclerosis Longitudinal Study, the team analysed the impact of variation in genes related to the vitamin D pathway. Treatment with IFN-β only increased levels of 25(OH)D in patients who carried one of two single nucleotide polymorphisms (SNPs) in the Wilms tumor 1 gene (*WT1*), a downstream component of the vitamin D receptor signal transduction pathway. Furthermore, one of these SNPs markedly reduced the IFN-β-enhancing effect of exposure to the sun.

Simpson says that the team expected IFN-β to target a more obvious component of the vitamin D pathway, such as vitamin D binding protein or 25-hydroxylase. "It seems that the actual pathway is more nuanced and may be more potent, given the many varied genes that the vitamin D receptor acts on in various cell types," he explains.

The results provide compelling evidence that the mechanism of IFN-β involves the vitamin D pathway. "We reaffirm that randomized controlled trials involving vitamin D and/or IFN-β should take both factors into account in evaluating their clinical efficacy," concludes Simpson.

Ian Fyfe

Original article Lin, R. *et al.* Modulating effects of *WT1* on interferon-β–vitamin D association in MS. *Acta Neurol. Scand.* doi:10.1111/ane.12315