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Influence of 25(OH)D levels and genetic variants on disease severity in MS

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Background:
Genetic variants linked to pathways related to vitamin D metabolism are associated with 25-hydroxyvitamin D (25[OH]D) serum levels in patients with MS. 25[OH]D levels were found to be inversely correlated with the cumulative number of newly active lesions (CNALES) in patients receiving interferon beta-1b in the BEYOND (Betaferon Efficacy Yielding Outcomes of a New Dose) trial in relapsing-remitting MS.
Objectives:
To examine the association of 25[OH]D levels with disease severity and activity in interferon beta-1b-treated patients in BEYOND and how these associations are modified by genetic variants related to vitamin D metabolism.
Methods:
For genome-wide association studies (GWAS), 662 patients with phenotypic and genotypic data available were split into three geographic regions to account for systematic differences in vitamin D levels. GWAS were conducted on imputed variants for each region separately, using ancestry components, sex, age, treatment, presence of anti-drug antibodies, and, where applicable, disease duration as covariates. Results were combined using fixed-effects pooled analyses and used for calculation of genomic inflation, followed by

examination of candidate variants. Variables assessed for associations include baseline MSSS (MS severity score, EDSS adjusted for disease duration), T2 lesion volume, and cerebral volume as well as annualized relapse count, change in EDSS, CNALES and change in cerebral volume over the 2-3.5 year period of the study. Analyses were carried out with and without including 25[OH]D levels.

Results:

MSSS and T2 lesion volume at baseline and CNALES over the course of the trial were significantly associated with 25[OH]D levels. Two candidate variants were significantly associated with MSSS, rs6599638 in the gene *C10orf88* (p=0.0003) and rs2248359 in *CYP23A1* (p = 0.002); the association of rs6599638 improved when 25[OH]D levels were accounted for (p = 0.00007). No significant interaction between either variant and 25[OH]D levels could be detected. Furthermore, no significant associations were found between candidate variants and T2 lesion volume or CNALES.

Conclusions:

MSSS at baseline of the BEYOND trial was associated with 25[OH]D levels. Significant associations between two candidate genetic variants linked to vitamin D metabolism and MSSS were identified. 25[OH]D levels had a significant effect on these models. These variants were not associated with disease progression during the trial.

Author disclosures

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- MF serves on scientific advisory boards for Teva and Genmab; has received funding for travel from Bayer Schering Pharma, Biogen-Dompé, Genmab, Merck Serono, and Teva; serves on editorial boards of the *American Journal of Neuroradiology*, *BMC Musculoskeletal Disorders*, *Clinical Neurology and Neurosurgery*, *Erciyes Medical Journal, Journal of Alzheimer's Disease, Journal of Neuroimaging*, *Journal of Neurovirology*, *Magnetic Resonance Imaging*, *Multiple Sclerosis*, and *Neurological Sciences*; serves as a consultant to Bayer Schering Pharma, Biogen-Dompé, Genmab, Merck Serono, and Teva; serves on speakers' bureaus for Bayer Schering Pharma, Biogen-Dompé, Genmab, Merck Serono, and Teva; and receives research support from Bayer Schering Pharma, Biogen-Dompé, Genmab, Merck Serono, Teva, and Fondazione Italiana Sclerosi Multipla
- DG has participated (or is currently participating) in several industry-sponsored clinical trials in MS. The sponsoring pharmaceutical companies for these trials have included (or do include) Ares-Serono, Merck Serono, Novartis, Berlex, Bayer Schering Pharma, Biogen Idec, Schering, and Teva Neuroscience. He has also lectured at both medical conferences and in public on various aspects of the epidemiology, diagnosis, and management of MS. In many cases, these talks have been sponsored directly or indirectly by one or another of the above-listed companies. He has also served as a temporary ad hoc consultant to several of these organizations on several occasions
- HPH has received honoraria for consulting and speaking at symposia from Bayer Pharma AG, Biogen Idec, Genzyme, GeNeuro, Octopharma, Merck Serono, Novartis, Roche, Teva, and Sanofi-Aventis, with approval by the rector of Heinrich-Heine University
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- BH served on scientific advisory boards for Roche, Novartis, Bayer Schering, Merck Serono, Biogen Idec, GlaxoSmithKline, Chugai Pharmaceutical, Genentech, and Genzyme Corporation; he serves on the international advisory board of Archives of Neurology and Experimental Neurology; he received speaker honoraria from Bayer Schering, Novartis, Biogen Idec, Merck Serono, Roche, and Teva Pharmaceutical Industries; he received research support from Biogen Idec, Bayer Schering, Merck Serono, Five Prime, Metanomics, Chugai Pharmaceutical, and Novartis. He has filed a patent for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and genetic determinants of neutralizing antibodies to interferon-beta
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