

We were hesitant to assign causality to this variant in *SBF1* even though its paralog *SBF2* plays a known role in the pathogenesis of autosomal recessive CMT. This is because of the highly discordant phenotype in *Sbf1*^{-/-} mice, which are phenotypically normal except for a spermatogenesis defect.³

Follow-up studies on humans showed that rare variants in *SBF1* are linked to male infertility.⁴ However, the findings of Nakhro et al. may confirm that *SBF1* is a disease gene for this condition. This is a reminder that model organisms cannot be the sole basis for rejecting the candidacy of disease genes in humans.

© 2014 American Academy of Neurology

1. Nakhro K, Park JM, Hong YB, et al. SET binding factor 1 (*SBF1*) mutation causes Charcot-Marie-Tooth disease type 4B3. *Neurology* 2013;81:165–173.
2. Bohlega S, Alazami AM, Cupler E, Al-Hindi H, Ibrahim E, Alkuraya FS. A novel syndromic form of sensory-motor polyneuropathy is linked to chromosome 22q13.31-q13.33. *Clin Genet* 2011;79:193–195.
3. Firestein R, Nagy PL, Daly M, Huie P, Conti M, Cleary ML. Male infertility, impaired spermatogenesis, and azoospermia in mice deficient for the pseudophosphatase *Sbf1*. *J Clin Invest* 2002;109:1165–1172.
4. Kuzmin A, Jarvi K, Lo K, et al. Identification of potentially damaging amino acid substitutions leading to human male infertility. *Biol Reprod* 2009;81:319–326.

UNRECOGNIZED VITAMIN D3 DEFICIENCY IS COMMON IN PARKINSON DISEASE: HARVARD BIOMARKER STUDY

Raja Mehanna, Houston: Ding et al.¹ concluded that a significant proportion of patients with Parkinson disease (PD) are vitamin D deficient, and the severity of deficiency is correlated to the severity and duration of the disease. The authors should be praised for admitting that this association does not mean causation and that PD might predispose to vitamin D deficiency by limiting outdoor activity. The authors should also be commended for not suggesting vitamin D supplementation to all patients with PD.

However, after the analysis was corrected for covariates, the overall relation between total 25[OH] vitamin D and PD was lost, but the authors considered the relation between 25[OH]D3 and PD at a *p* value of 0.047. Even though this is close to the 0.05 cutoff, the authors did not mention any correction for multiple statistical analyses, which may have affected the value of *p* and

rendered this relation not statistically significant. Ultimately, this could affect the conclusion that their study “reveals an association between 25[OH]D3 and PD.”

Author Response: Clemens R. Scherzer, Hongliu Ding, Joseph J. Locascio, Boston: We thank Dr. Mehanna for commenting on our study, where we used liquid chromatography/tandem mass spectrometry to investigate an association specifically between deficiency of the transcriptionally active human hormone 25[OH]D3 and PD. Our goal was to directly measure 25[OH]D3.

We chose this method because it is advantageous compared to other methods that assay total 25[OH]D (a composite measure of 25[OH]D2 and 25[OH]D3). Total 25[OH]D may be confounded by exogenous vitamin 25[OH]D2 that is not produced in humans but ingested through diet or supplements. In the primary analysis, plasma levels of 25[OH]D3 were associated with the prevalence of PD with an unadjusted *p* value of 0.0034 and a *p* value of 0.047 after adjusting for the baseline inequalities including age, sex, race, and vitamin D supplementation.

Dr. Mehanna noted that we did not mention any correction for multiple hypothesis testing and speculated that this may have affected the value of *p* and rendered the relation between 25[OH]D3 and PD not statistically significant. Although the adjusted *p* value of 0.047 is from a multivariate test (i.e., 25[OH]D3 adjusted for important covariates), it is from only one test: one *p* value that specifically answered the predefined primary scientific question. We agree with Dr. Mehanna that adjustment for multiple testing in the appropriate settings is vital^{2,3} but it does not apply here.

The data shown in our study, consistent with several previous independent cross-sectional and prospective investigations, confirm the view that vitamin D deficiency is both common and significant in PD.

© 2014 American Academy of Neurology

1. Ding H, Dhima K, Lockhart KC, et al. Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. *Neurology* 2013;81:1531–1537.
2. Scherzer CR. Chipping away at diagnostics for neurodegenerative diseases. *Neurobiol Dis* 2009;35:148–156.
3. Henneke G, Scherzer CR. RNA biomarkers of Parkinson's disease: developing tools for novel therapies. *Biomark Med* 2008;2:41–53.

Author disclosures are available upon request (journal@neurology.org).

Neurology®

Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study

Raja Mehanna, Clemens R. Scherzer, Hongliu Ding, et al.

Neurology 2014;82;1666

DOI 10.1212/01.wnl.0000449750.81263.7d

This information is current as of May 5, 2014

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/82/18/1666.full
References	This article cites 3 articles, 1 of which you can access for free at: http://n.neurology.org/content/82/18/1666.full#ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2014 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

