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.

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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.

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