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Peripheral neuropathy risk and a transcobalamin polymorphism: connecting the dots between excessive folate intake and disease susceptibility

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Advances in the broad field of nutritional genomics continue to shed light on variable disease susceptibility to modifications in micronutrient intake within populations. This is certainly the case within the field of one-carbon metabolism and its ensemble of B vitamins, as is abundantly clear from the plethora of scientific publications focused on this topic that have been reported in the pages of this Journal and elsewhere. The sometimes puzzling and even conflicting associations that have been reported may be explained by differences in sample sizes, cross-sectional study design, micronutrient intake, and population heterogeneity. Further adding to the complexity of gene-nutrient interactions and their effects on disease susceptibility and severity are the constellations of interactive polymorphisms in one-carbon metabolism, together with substrate and cofactor availability, all of which may affect resultant phenotypes (1). The article by Sawaengsri et al. (2) in this issue of the Journal, which reports that the common 776C→G polymorphism in the transcobalamin (*TCN2*) vitamin B-12 transporter gene is associated with peripheral neuropathy in elderly individuals with high folate intakes, informs on the currently vexed question of folate fortification and supplement use.

The findings by Sawaengsri et al. are timely and complement the recent report by Brito et al. (3), also in the Journal, that improvement in peripheral nerve conduction by vitamin B-12 supplementation of elderly subjects deficient in the vitamin was impaired by high serum folate status in a Chilean population who consumed a diet containing twice the level of folic acid fortification practiced in the United States. As more information accumulates about the potentially deleterious effects of excessive folate intake, it would seem prudent to re-examine current complacencies about the safety of high folate intake, particularly through the use of folic acid supplements (4).

Despite the clear message from the work of Sawaengsri et al. with regard to caveats concerning excessive folate intake, particularly among the elderly, fundamental aspects of their reported findings must await further elucidation. What is the mechanism responsible for the increased susceptibility to impaired peripheral nerve function in individuals homozygous for the *TCN2* 776C→G polymorphism, and why do higher folate intakes aggravate this condition? These fundamental questions will be difficult to answer, and at this time, speculation must suffice. The authors posit that lower transcobalamin (TC) protein concentration as well as impaired binding of vitamin B-12 by the variant enzyme might be responsible for the phenotypic consequences of the polymorphism. However, other explanations may also apply, including the possibility that *TCN2* genotype has an effect on the binding of the protein to the TC receptor. Although Sawaengsri et al. did not observe a relation between the *TCN2* polymorphism and plasma concentrations of total homocysteine, others have reported that homocysteine concentrations were actually higher for 776CC homozygotes than for carriers of the G allele (776CG and 776GG combined) when total vitamin B-12 or holo-TC concentrations were low (5). From this it could be argued that the G allele might actually be protective rather than deleterious when vitamin B-12 status is low, and this potential survival advantage under conditions of vitamin B-12 privation could explain the relatively high prevalence of the variant form observed in different populations. As to the interactive role of high folate, this still remains a mystery.

Given the apparent increased susceptibility of individuals who are homozygous for the *TCN2* 776GG variant to peripheral nerve dysfunction, the question arises whether the same association might apply to the central nervous system. In particular, it would be important to know whether *TCN* genotype confers risk or protection with regard to the age-related decline in cognitive function and brain atrophy. These pathologies have been shown to relate to substrate supply and metabolite accumulation in the complex nexus of one-carbon metabolism (6). In this regard, it was reported in a relatively small cohort of patients that *TCN2* genotype may influence the age of onset of Alzheimer disease because 776GG homozygosity was associated with younger age of onset (7). This association will need to be confirmed in a larger study, in light of the findings by Sawaengsri et al. and taking into consideration folate intake. The authors' conclusion that the *TCN2* 776C→G polymorphism was associated with increased odds for peripheral neuropathy despite normal vitamin B-12 status, especially if folate intake was in excess of twice the Recommended

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First published online November 16, 2016; doi: 10.3945/ajcn.116.146365.

Dietary Allowance, opens wide the Pandora's box of unanticipated hazards, most notably neurological, that may be associated with excessive folate, and in particular folic acid, intake.

The author had no conflicts of interest to declare.

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