Correspondence

Immunoglobulin κ Chain Locus on Chromosome 2p12 and Onchocerciasis

To the Editor—Although the genome-wide linkage study by Timmann et al. provides compelling evidence for the presence of a gene (or genes) on chromosome 2p influencing resistance to *Onchocerca volvulus*, they state, “The genes located in the linkage interval do not include an obvious functional candidate” [1, p. 431]. I would like to draw attention to a study that suggested the presence of a functional candidate gene for influencing resistance to *O. volvulus* on chromosome 2p over a decade ago.

In 1995, an association study by Pandey et al. that used a candidate gene approach showed that the gene encoding the immunoglobulin κ light chain, the KM locus on chromosome 2p12, might be involved in the pathogenesis of onchocerciasis, a disease caused by *O. volvulus* [2]. We reported that in Afro-Ecuadorians, homozygosity for the KM 3 allele was associated (*P* = .001) with putative immunity to onchocerciasis, whereas heterozygosity (KM 1,3) was associated (*P* = .004) with an increased risk of developing the disease. Furthermore, the results of this study indicated the presence of racial genetic heterogeneity in the outcome of infection with *O. volvulus*, because the KM phenotypes were not associated (*P* = .283) with the risk of onchocerciasis in Amerindians living in the same onchocerciasis-hyperendemic area of Ecuador.

The KM alleles are functional in that they could contribute to interindividual differences in the outcome of infection with *O. volvulus* by influencing humoral immunity to this nematode, as shown for other infectious agents [3–5]. Perhaps B cell membrane-bound IgG molecules with KM 3 light chains act as more compatible receptors for *O. volvulus* and thus provoke a strong humoral immunity, whereas IgG molecules with KM 1,3 form a less compatible receptor for the critical epitopes of this infectious agent.

In view of the results reported by Timmann et al. [1] and Pandey et al. [2], large-scale linkage and association studies in diverse population groups—employing genetic makers between 2p21 and 2p12 regions—are warranted to identify genes involved in the etiopathogenesis of onchocerciasis, a leading cause of blindness that affects >18 million people worldwide [6].

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References

Reply to Pandey

In their 1995 article, Pandey et al. [1] presented evidence for allotypes of the immunoglobulin κ chain locus (IGK/IGKC) or an unknown major locus in tight linkage disequilibrium on chromosome 2p12 being associated with putative immunity in Afro-Ecuadorians, but not in Amerindians. In our recent genome-wide study [2], we described significant linkage between infection intensity and the chromosomal region 2p21 to 2p14 (Ov1) in a Ghanaian population. Ov1 is located at marker position D2S2378, corresponding to 70.31 cM/46.1 Mb. The 1-LOD support interval encompassed from 2p21 to 2p14 (15 cM/17.5 Mb) between markers D2S2298 (69 cM/44 Mb) and D2S337 (84 cM/61.5 Mb). The IGK/IGKC (112 cM/89 Mb) shows a genetic distance of 28 cM and a physical distance of 27.5 Mb from the centromeric extension of the 1-LOD support interval of Ov1, and is therefore not supported by our study. These different findings may be attributable to extended genetic differences and heterogeneity within and between West African and Ecuadorian populations.

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Potential conflicts of interest: none reported.

Financial support: National Institutes of Health grant DK070877.

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*The Journal of Infectious Diseases* 2009; 199:286
© 2009 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2009/19902-0018$15.00 DOI: 10.1086/595741
Potential conflicts of interest: none reported.

Financial support: Deutsche Forschungsgemeinschaft (grant HO 886/4-1), Volkswagen Foundation, Germany.

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The Journal of Infectious Diseases 2009;199:286–7
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DOI: 10.1086/595742

Nutrient Supplementation and Tuberculosis Treatment Outcome

To the Editor—We read with great interest the recent article by Villamor et al. [1] on the effect of micronutrient supplementation on tuberculosis (TB) treatment outcome as well as the accompanying editorial commentary by Benn et al. [2]. It is well known that TB is associated with being underweight [3]. Nutritional deficiency has also been found to be a negative prognostic factor in patients with miliary TB [4]. Being underweight at baseline [5] and the absence of early gain weight [6] have been associated with an increased risk of relapse in a large-scale TB treatment trial. However, relatively few studies have specifically examined the effect of nutrient supplementation.

The randomized controlled trial design, as rightly adopted by Villamor et al., is indispensable for obtaining a definitive answer regarding the role played by nutritional supplementation. However, as was pointed out in the accompanying editorial, micronutrients benefited HIV-uninfected subjects the most in Villamor et al.’s trial, whereas the opposite was the case in a previous trial in Tanzania [7]. Differences in case mix and study design could be contributing factors.

In anti-TB chemotherapy, bacteriological cure with the absence of relapse is probably the most clinically relevant end point. Although it is generally acceptable to use validated surrogate end points, such as 2-month culture conversion [8] or time to culture conversion [9], to decrease the sample size requirement and to shorten the duration of follow-up in explorative trials, caution has to be exercised in the employment of less-well-characterized end points, such as culture reversion after a single negative sputum culture result during the first month. Minor variation in sputum-collection technique and/or sputum processing could have produced a single negative culture result when the bacillary load was low after a month of treatment. When multiple end points and subgroups are evaluated in a single trial, results should also be interpreted with care.

Given that TB is generally more prevalent in developing areas and that nutritional supplementation is likely to show the greatest effect among those with malnourishment, an adequately powered trial will probably have to be implemented in a resources-limited area. Although specific nutrients might play a role, the overall nutritional status as reflected by body mass index also appears to greatly influence the risk of TB [3]. It is, therefore, necessary to study the effects of—or at least control for—the effect of overall nutritional status in nutrient-supplementation trials. Careful documentation of the overall nutritional status, in addition to specific nutrient deficiencies, is desirable, so that a maximum amount of information can be extracted from these often-costly trials.

The interaction between nutritional status and TB is complex. TB is also well known for its wasting effects. Dietary supplementation may fail either because of poor adherence or overwhelming disease effect. It may, therefore, be useful to monitor the relevant nutritional parameters during the intervention. Because sustained inflammatory disease activity may negate the effect of simple nutrient supplementation, at least in some patients, the role played by adjunctive corticoste-roides might also merit reappraisal. Indeed, such treatment has been found to afford earlier and more significant body weight gain, albeit with no differences in sputum bacteriological conversion and disease relapse rate [10].

Anti-TB drug resistance is an increasing concern globally. With our currently limited armament, it might be difficult to work out an effective regimen for those patients who have extensively drug-resistant TB. Because only 1 in 10 infected persons, on average, will ever develop disease in his or her lifetime, host factors appear to be critical in the defense against the tubercle bacillus. In situations where we are almost back to the prechemotherapy era, it might also be worthwhile to reexamine the role played by nutritional supplementation, either alone or as an adjunct to chemotherapy and/or surgery, in the humanitarian and active management of TB disease in these unfortunate patients.

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