LETTER

REPLY TO GILCHRIST ET AL.:

Possible roles for *VAC14* in multiple infectious diseases

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Our studies of the SNP rs8060947 determine that the A allele is associated with increased invasion of *Salmonella enterica* serovar Typhi and increased susceptibility to typhoid fever (1). Gilchrist et al. (2) now provide evidence that the A allele is also associated with increased risk for bacteremia, and the association was driven primarily by nontyphoidal *Salmonella*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Acinetobacter*, but not by *Staphylococcus aureus*, β-hemolytic streptococci, or *Haemophilus influenza* type b. Future studies are necessary to further validate the association between *VAC14* and infectious diseases, determine the molecular mechanisms of protection, and investigate the possible evolutionary forces that have acted at this locus.

As our functional studies of *VAC14* demonstrate a mechanism involving altered plasma membrane cholesterol content, we examined whether the bacterial pathogens implicated by Gilchrist et al. (2) have previously been demonstrated to require cholesterol to invade or cause disease. Interestingly, there is literature indicating cholesterol is necessary for *Salmonella* and *E. coli* invasion (3, 4), as well as literature showing that *S. pneumoniae* and *Acinetobacter* toxins require cholesterol for entry into cells (5, 6). Notably the effects of rs8060947 are in the same direction; the A allele has higher association with typhoid fever (1) and bacteremia (2), consistent with each of these pathogens, or the toxins they produce, having cholesterol-dependent entry. Moreover, for the pathogens that did not show an association with rs8060947 in their analysis, we could not find data to suggest that cholesterol is necessary for *S. aureus* or *H. influenzae* to establish disease, although β-hemolytic streptococci have been shown to require cholesterol for the entry of its toxins (7). Therefore, a cholesterol-dependent mechanism of protection is consistent for multiple bacterial pathogens, but awaits further mechanistic testing.

The G allele of rs8060947 is ancestral and protective, but the A allele has higher frequency in Europe and Asia (Fig. 1). This is counterintuitive, given the importance of pathogens in driving natural selection in humans (8) and the apparent increased susceptibility to bacterial pathogens due to the A allele. Therefore, we speculate there may be counteracting evolutionary pressures for maintenance of the A allele. While in our previous paper (1) we provide evidence for *VAC14* regulating cellular cholesterol levels, *VAC14* has other well-documented cellular functions. VAC14 knockout cells have characteristically enlarged vacuoles due to impaired endosomal trafficking (9). Additionally, mutations in the VAC14 protein complex lead to impairment of neuronal development and trafficking in humans (10). We do not know whether rs8060947 affects these functions of VAC14. Additionally, we do not know whether the A allele may actually be protective against other pathogens, but we are currently testing this idea.

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The authors declare no conflict of interest.

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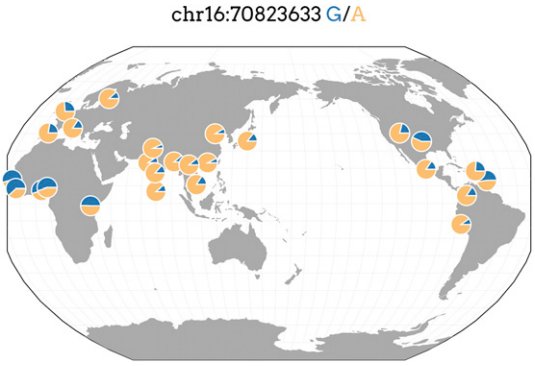

Fig. 1. Geographic distribution of SNP rs8060947.The G allele is ancestral and protective against certain bacterial pathogens; the A allele is derived and associated with susceptibility. Map generated from the Geography of Genetic Variants Browser (11).

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