Genetic variation in *VAC14* is associated with bacteremia secondary to diverse pathogens in African children

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Performing a genome-wide association study of *Salmonella enterica* serovar Typhi (*S.* Typhi) invasion, Alvarez et al. (1) identify a trait-associated SNP, rs8060947, in *VAC14*. rs8060947 is an expression quantitative trait locus for *VAC14* RNA expression, and carriage of the A allele is associated with reduced *VAC14* RNA and protein expression, and increased invasion of *S.* Typhi. VAC14-associated inhibition of *S.* Typhi invasion is mediated by a reduction in host cell membrane cholesterol. Carriage of the A allele at rs8060947 is associated with typhoid fever in Vietnamese individuals [cases = 496, controls = 500; $P = 0.01$, additive odds ratio (OR) = 1.38]. The authors further identify a SNP in high linkage disequilibrium with rs8060947 and rs8044133, located in a transcription factor binding site, which merits further investigation as the causative SNP.

Alvarez et al. (1) note that cholesterol has been implicated in the invasion and pathogenesis of a wide range of pathogens (2–5). We therefore used previously published genome-wide association study data, describing susceptibility to bacteraemia secondary to diverse pathogens in Kenyan children (6), to explore whether genetic variation at the *VAC14* locus is associated with susceptibility to invasive bacterial infections other than typhoid fever. In Kenyan children (cases = 1,536, controls = 2,677), rs8060947 (Fig. 1*A*) is significantly associated with all-cause bacteremia: $P_{additive} = 0.02$, OR = 1.11 [95% confidence interval (CI) 1.02–1.22]. In keeping with the effect observed in typhoid, carriage of the A allele at rs8060947 increases risk of bacteremia.

To understand whether risk of bacteremia conferred by rs8060947 is shared across pathogens causing bacteremia in Kenyan children, we conducted a Bayesian analysis comparing models of association at rs8060947 with the major causes of bacteremia in this population (Fig. 1*B*). The most probable model is one in which rs8060947 is associated with susceptibility to bacteraemia caused by nontyphoidal *Salmonella* (NTS), *Streptococcus pneumoniae*, *Escherichia coli*, and *Acinetobacter* species, but not bacteremia caused by other pathogens (Fig. 1*C*). We performed imputation-based mapping of the association at the *VAC14* locus with bacteremia secondary to NTS, *S. pneumoniae*, *E. coli*, and *Acinetobacter* species (Fig. 2). In that analysis, there is evidence for association between bacteremia secondary to these four pathogens and both rs8060947 [$P_{additive} = 4.76 \times 10^{-3}$, OR = 1.17 (95% CI = 1.05–1.30)] and rs8044133 [$P_{additive} = 4.58 \times 10^{-3}$, OR = 1.17 (95% CI = 1.05–1.30)].

Alvarez et al. (1) demonstrate that genetic variation in *VAC14* is a determinant of clinical typhoid fever in Vietnamese individuals. Our data expand on this observation, demonstrating that the same risk allele at rs8060947, with a comparable effect size, increases risk of bacteremia secondary to diverse pathogens in Kenyan children. This observation may reflect a previously unrecognized role for cholesterol in the pathogenesis of diverse bacterial pathogens, or a role for cholesterol in a shared risk factor for these pathogens in this population (e.g., malaria or HIV). Future studies will be required to further define the range of clinical diseases associated with *VAC14*, and to fine-map the genetic signal at *VAC14*.

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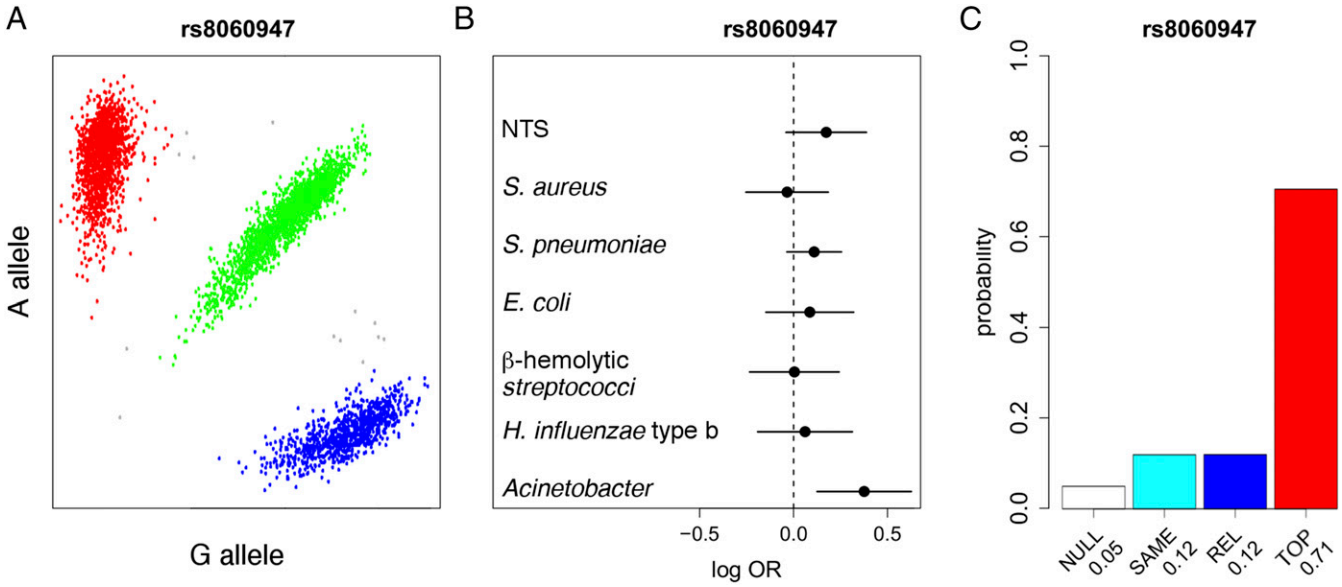

Fig. 1. rs8060947 and major causes of bacteremia in Kenyan children. (*A*) Cluster plot of rs8060947 (Affymetrix SNP 6.0 chip) in Kenyan children (*n* = 4,924); minor allele frequency (MAF) = 0.44, Hardy–Weinberg equilibrium (HWE) *P* = 0.11. (*B*) rs8060947 association with major causes of bacteremia in Kenyan children; NTS, *n* = 180, *Staphylococcus aureus*, *n* = 175, *S. pneumoniae*, *n* = 426, *E. coli*, *n* = 151, β-hemolytic *Streptococci*, *n* = 146, *Haemophilus influenza* type b, *n* = 128, *Acinetobacter* species, *n* = 130. Log-transformed ORs and 95% CIs of rs8060947 association (additive model) are calculated by multinomial logistic regression, including four principal components of genome-wide genotyping data to account for population structure. (*C*) Posterior probabilities of models of association at rs8060947: NULL, no association with any pathogen; REL, related effects ∼ N(0,0.2^2) across all pathogens (correlation is ρ=0.96); SAME, the same effect ∼ N(0,0.2^2) across all pathogens (correlation is ρ = 1); TOP, a nonzero effect in bacteremia secondary to nontyphoidal *Salmonella*, *E. coli*, *S. pneumoniae*, and *Acinetobacter* species alone; this model (highlighted in red) is the most probable (Bayes factor c.f. NULL = 14). Genotype and phenotype data are derived from Rautanen et al. (6). Methods are as described in Rautanen et al. (6).

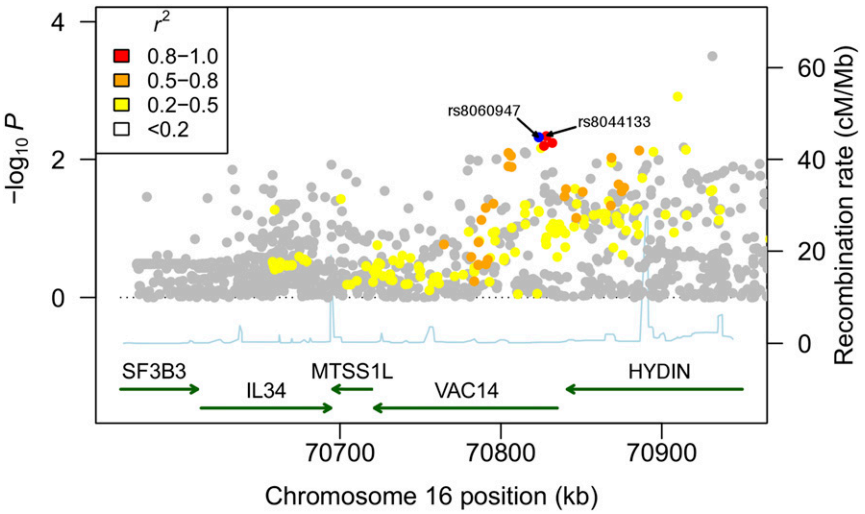

Fig. 2. Association plot of bacteremia susceptibility at the *VAC14* locus. SNPs are colored according to strength of linkage disequilibrium (r^2) to rs8060947. Association statistics are calculated using an additive model including bacteremia cases secondary to NTS, *E. coli*, *S. pneumoniae*, and *Acinetobacter* species ($n = 887$) and shared, healthy controls ($n = 2,677$). rs8044133 is imputed (imputation information score = 0.996), MAF = 0.47, with no evidence of departure from HWE ($P = 0.73$). Common (MAF > 0.05), well-imputed SNPs (imputation information score > 0.4), with no evidence for departure from HWE ($P > 1 \times 10^{-10}$) were included in the analysis. Association statistics are calculated by logistic regression, including four principal components of genome-wide genotyping data to account for population structure. Genotype and phenotype data are derived from Rautanen et al. (6). Methods are as described in Rautanen et al. (6).

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