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COMMENTARY

Genetic variation in response to a typhoid vaccine

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Typhoid fever, due to *S. typhi* bacterial infection, results in an estimated 200,000–600,000 deaths in the developing world each year (Sur et al. 2009). Recognition that expression of the Vi polysaccharide encapsulating *S. typhi* is a major determinant of virulence has lead to the development of a ViPS vaccine which is marketed in many developing countries. Recent studies have shown that when this vaccine was introduced into an area in India where typhoid fever is endemic, it conferred 61% total protection in the general population, without evidence of increased selection of Vi-negative strains or increased antibiotic resistance (Sur et al. 2009). However, little is known concerning the genetic and environmental factors that are associated with ViPS vaccine failure. There is evidence that ethnicity can play an important role in the immunological response to certain polysaccharide antigens, and that genetic factors appear to play a particularly large role for vaccine-induced antibody responses in young children (Kimman et al. 2007). Increased knowledge of specific genetic determinants that impact individual immunological response to the ViPS vaccine will be important for the design of next-generation vaccines with even broader efficacy across diverse populations. In this issue of the journal, Majumder and colleagues describe their efforts to identify genetic determinants associated with variability in antibody response following ViPS vaccination in 984 Indian individuals resident in an area high-risk for typhoid fever (Majumder et al. 2010). This study represents one of the first efforts to identify specific genetic factors responsible differential immune response to a polysaccharide vaccine, and it provides instructive lessons for future research in this area.

VIPS-specific antibody levels were measured in each individual pre- and 28 days post-vaccination, and the difference in specific-antibody response (AR) was quantified. Large individual differences in the levels of pre- and post vaccination ViPS specific- antibody were observed, but there was a very low correlation between the pre- and post vaccination antibody levels in any given individual. Differences in AR could not be explained by variation in age, gender, or religion. Values of AR were log-transformed to obtain a normal frequency distribution. A candidate gene association study was then performed to identify genetic variants associated with logAR, using 469 independent common SNPs with minimal linkage disequilibrium and representing 282 genes present in immunological pathways. It is well accepted that any result from such a candidate gene association study requires independent replication, preferably involving multiple different ethic groups. In this case, no additional independent population was available for study, so the authors employed a "non-standard" internal cross-validation design employing correlation of SNP minor allele frequencies with logAR mean values distributed into pentile groups. The 984 vaccinees were randomly split into two half-samples of approximately 500 individuals each, with the first half-sample used to identify 54 SNPs in 43 genes significantly associated with variation in immune response, and the second-half sample used to demonstrate significant replication of 8 of these SNPs in 7 genes. All eight significant SNPs are intronic. For six of the eight significant SNPs, an increase in the minor allele frequency with associated with an increased antibody response, while for two of the significant SNPs, increasing the minor allele frequency was associated with a decreased antibody response. Each of

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these eight SNPs was also shown to be significantly associated with antibody response using PLINK and a more standard quantitative trait association analysis employing the entire data set. A haplotype analysis identified an additional 8 SNPs which were associated with log AR. The seven genes containing significantly associated SNPs are known to be involved in polysaccharide recognition, signal transduction, inhibition of T-cell proliferation, and pro-inflammatory signaling.

What are the lessons we can learn from this study? The first is that each significantly associated common SNP had a very small effect on the overall antibody response following vaccination. Similar observations now seem to be the rule, rather than the exception, for a wide range of complex phenotypes investigated using genome wide association analysis. For phenotypes where tens of thousands of study subjects are available, it is possible to obtain highly significant associations replicated in multiple populations for common variants with a very small genetic effect. But what about phenotypes such as the one studied by Majumder et al. (2010), where obtaining a single population sample of a thousand individuals is a tremendous feat in itself? It will often be necessary to employ "non-standard" but statistically rigorous approaches, as in the present study, to identify small genetic signals, which will often be of marginal statistical significance. The true value of such results lies not in the size of the p value, but in the ability to use the results to generate meaningful hypotheses and experiments to determine the biological basis of the differences in antibody response. Only with this type of biological understanding in hand will the ultimate goal of designing more effective vaccines be realized. The second lesson learned is that in studies involving clinical outcomes, where each sample is precious and difficult to come by, we should make every effort obtain as much detailed phenotypic information as possible from each subject. While the present study demonstrates marked variability in antibody response to vaccination, similar studies with other polysaccharide vaccines have found that the ability of an individual to mature antibody avidity, rather than simply respond with a quantitative increase in antibody, is very important for vaccine efficacy (Lee et al. 2008). It would have been interesting to know if subjects in this study show differences in antibody avidity, and if so, if there were any genetic correlates associated with this trait. Finally, and perhaps most importantly, the present study reveals how important it is to address basic research questions dealing with rare clinical outcomes in the context of ongoing clinical trials. A recent study assessing the Vi typhoid vaccine efficacy in India involved 37,673 study subjects and found only 34 individuals in the Vi vaccine group who developed typhoid fever despite Vi vaccination, compared to 96 subjects who developed typhoid fever in the control group (Sur et al. 2009). The ability to assess these individuals for differences in immunological response would be invaluable as a complement to the present study. It is impossible to identify such individuals outside the context of a clinical trial.

Development of next-generation vaccines that have high levels of efficacy in diverse populations residing in developing countries is a huge challenge. Pioneering efforts, as illustrated by the work of Majumder et al. (2010) are definitely a step in the right direction.

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