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Immunoglobulin GM and KM Alleotypes and Antibody Responses to Epstein-Barr Virus Antigens

To the Editor—Besson et al [1], in their study of first-degree relatives from families with Epstein-Barr virus (EBV)–related lymphomas, provide strong evidence for polygenic inheritance of the ability to generate antibodies to the EBV viral capsid antigen (VCA), and they conclude that these results “pave the way for identification of the loci involved” [1, p 1121]. I would like to draw attention to a 25-year-old study that suggested that immunoglobulin loci are involved in antibody responsiveness to several EBV antigens.

In 1984, a study by Biggar et al [2] showed that immunoglobulin GM and KM alleotypes—genetic markers of γ and κ light chains, respectively—interact in a complex manner to influence the antibody responses to EBV antigens. My colleagues and I showed that, in patients with Burkitt lymphoma, simultaneous homozygosity or heterozygosity at GM (chromosome 14) and KM (chromosome 2) loci resulted in higher antibody responses to EBV antigens than did dissimilar zygosity at the 2 loci. These results—coupled with the substantial heritability for anti-VCA immunoglobulin G (IgG) antibodies reported by Besson et al [1]—provide a strong rationale for large-scale studies to examine the role played by immunoglobulin GM and KM genes in humoral immunity to EBV antigens. Such studies must include diverse population groups, because major races are characterized by unique arrays of GM haplotypes and because KM gene frequencies also vary significantly among various groups [3]—therefore, associations obtained in one racial group may not be transferable to another group.

I would also like to add a cautionary note concerning “the identification of genes involved in controlling anti-VCA IgG levels, through genomewide linkage and association studies” suggested by Besson et al [1, p 1127]. At present, commonly used genotyping platforms in most genomewide linkage and association studies do not include immunoglobulin genes. The HapMap catalogue—a major source of guidance for the inclusion of single-nucleotide polymorphisms (SNPs) in the commercial genotyping platforms—does not include SNPs in the immunoglobulin region, nor do the SNPs in the catalogue tag these immunologically important genes. Thus, for now the term genomewide is a misnomer, because the commercial genotyping platforms do not tag rare SNPs and because a significant portion of common SNPs are only partially tagged or not tagged at all, providing one explanation as to why most of the heritability of complex traits remains unexplained by these so-called genomewide studies [4, 5]. Furthermore, to date genomewide association studies have been very unproductive in detecting epistasis (modification of the action of a gene by 1 or more other genes), and the study by Biggar et al [2] suggested that epistatic interactions between GM and KM alleles contribute to anti-EBV antibody responses. Therefore, until more-complete genotyping platforms are available and the methods to more-adequately measure epistasis in genomewide association studies have been developed, a candidate gene approach—using GM, KM, HLA, and other genes of the immune system—is likely to be more rewarding and may shed some light on the host genetic mechanisms involved in the pathogenesis of EBV-related lymphomas.

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