EDITORIAL COMMENTARY

Genetics and Infectious Mononucleosis

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(See the Major Article by Rostgaard et al on pages 1684–9.)

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The epidemiology of primary Epstein-Barr virus (EBV) infection is not completely understood. We know that kissing is the major route of transmission of primary EBV infection among teenagers and young adults [1], but we do not know the mechanism(s) of transmission among preadolescent children. In addition, we do not know why the majority of primary EBV infections in young children go unrecognized [2], whereas those in adolescents and young adults usually result in infectious mononucleosis (IM) [1]. We also do not know whether it is better to get infected by EBV early in life or later on. Evidently, much remains to be learned about the enigmatic epidemiology of EBV, but we now have some compelling information that genes are involved. In this issue of Clinical Infectious Diseases, Rostgaard and colleagues tracked familial clustering of hospitalized cases of IM [3]. Using very large Danish national databases, these investigators reported that same-sex twins had a rate ratio of 9.3 for mono, compared with 2.3 for first-degree relatives (opposite-sex twins, siblings, and parents), 1.4 for second-degree relatives (half-siblings, grandparents, uncles, and aunts), and 1.0 for third-degree relatives (first cousins). The 95% confidence intervals for those 4 classes of relationships did not overlap, supporting the conclusion that degree of relatedness increased the likelihood of contracting mono.

Hwang et al, utilizing the California Twin Program registry, reported that concordance for IM in monozygotic twins was twice that of dizygotic twins [4]. They interpreted their results as consistent with a genetic contribution to susceptibility to mono. Twins certainly share the same environment and likely have similar behavioral factors. However, the significantly greater number of cases in monozygotic or same-sex twins vs dizygotic or opposite-sex twins in both the California and the Danish studies is compelling evidence that susceptibility to IM has a genetic component.

A strength of both studies was the large size of the cohort investigated. A limitation of the Danish study was that only relatively severe IM was captured (85% of the cases were inpatient admissions), and therefore the results may not be applicable to typical outpatient cases of mono. Shortcomings of both studies include the lack of laboratory confirmation of EBV infection, and few data on racial groups other than whites.

Rostgaard and colleagues suggest that genome-wide association studies might uncover EBV susceptibility loci that not only confer a risk for IM but also for development of EBV-associated cancer or autoimmune disease. Including diverse racial/ethnic groups in such investigations could broaden our ability to discover important genetic variants associated with acquisition, severity, and sequelae of EBV infection. In support of this, 2 separate cross-sectional surveys of US children found that early acquisition of EBV infection, as evidenced by having antibodies against EBV viral capsid antigen, was a racial disparity that could not be satisfactorily explained by socioeconomic factors alone [5, 6]. The enormous difference in overall age- and sex-adjusted EBV antibody prevalence between non-Hispanic white (32%) and non-Hispanic black children (62%) in the study by Condon et al [6] is consistent with a genetic basis for the racial clustering of EBV infection in younger children.

A history of IM predisposes to Hodgkin lymphoma [7] and multiple sclerosis [8]. Why? A plausible explanation is that more severe primary EBV infection reflects dysregulated immune control of the virus (probably due to the host’s genetic makeup), which persists during viral latency, eventually leading to EBV-associated malignancy or autoimmune disease.

Rostgaard and colleagues have told us that susceptibility to symptomatic EBV

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infection is genetically influenced. Our challenge now is to find a candidate genetic marker that identifies individuals in jeopardy for serious EBV disease so that we can recognize them and potentially intervene before they get sick. These individuals would greatly benefit from a prophylactic EBV vaccine, and such vaccines are now in development [9].

Notes

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