Infectious Disease Genomics: Individual Variability, New Opportunities

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Technological advances now enable comparisons of more than 500,000 genetic variants in subjects with disease and population controls. A large number of novel genetic loci that are involved in susceptibility to common immune-related diseases, such as rheumatoid arthritis and inflammatory bowel disease, have been identified through genomewide association studies (GWAS). More recently, this methodology has been successfully applied to identify loci that are involved in infectious disease susceptibility [Vannberg FO et al. *Immunol Rev* 2011]. David B. Goldstein, PhD, Duke University School of Medicine, Durham, North Carolina, USA, discussed recent studies, challenges, and next steps in infectious disease genomics.

According to Dr. Goldstein, susceptibility to pathogens is a genetic trait, with heritability as high as the most heritable diseases. He emphasized that, so far as can be discerned, there are differences amongst people in their response to all known pathogens; citing findings from studies on the hepatitis C virus (HCV) as examples.

Chronic infection with HCV affects 170 million people worldwide and is the leading cause of cirrhosis in North America. The recommended treatment involves a 48-week course of peginterferon-alpha-2b (PegIFN-alpha-2b) or alpha 2a (PegIFN-alpha-2a), combined with ribavirin (RBV)—an expensive process that is accompanied by significant adverse effects, (eg, anemia) that prevent some patients from completing treatment [Ge D et al. *Nature* 2009].

Many patients are not cured by treatment, and those with European ancestry have a significantly higher probability than patients of African descent of achieving sustained virological response (SVR) [Ge D et al. *Nature* 2009]. Response rates to pegIFN and RBV are also lower for Latino Americans and for those who are coinfected with HIV [Rodriguez-Torres M et al. *N Engl J Med* 2009]. East Asians, however, have higher SVR rates than patients of European ancestry [Yan KK et al. *World J Gastroenterol* 2008].

SVR Rates and rs12979860 on Chromosome 19

In a GWAS, Ge et al. [*Nature* 2009] reported that a genetic polymorphism on chromosome 19, rs1297860, was strongly associated with SVR in all patient groups, with the Caucasian population sample showing overwhelming genomewide significance ($p=1.06 \times 10^{-25}$) versus that seen in African-Americans ($p=2.06 \times 10^{-3}$). It is also known that the variants that are associated with SVR also influence natural clearance.

In patients with HCV genotypes 2 or 3 (n=341) who were treated with 12 or 24 weeks of pegIFN/RBV therapy, rs12979860 determined the first phase of viral elimination ($p<0.001$). In patients who were treated for 24 weeks, rs1279860 also predicted the rate of SVR ($p=0.02$), especially in those with high baseline hepatitis C virus ribonucleic acid (HCV RNA levels ($p=0.02$) or aged >45 years ($p=0.01$). Patients who carried the CC genotype had higher baseline HCV RNA levels ($p<0.001$). When treated for 12 weeks, they did not achieve SVR more often than those who were carrying CT or TT genotypes.

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The results indicate that IL28B gene testing may identify HCV genotype 2 or 3 patients who could benefit from extended treatment [Lindh M et al. *J Infect Dis* 2011]. IL28B genotyping could also aid in PegIFN/RBV clinical decision-making and may be useful in the selection of candidates for triple therapy with PegIFNB/RBV plus direct-acting antiviral drugs [Marcias J et al. *Curr Opin HIV AIDS* 2011].

In a recent study of HCV, 4 patients who were treated with PegIFN/RBV, 49% achieved an SVR (88% in CC patients vs 37% in CT/TT patients; p<0.0001). CC patients had a rapid virologic response (RVR) more often than CT/TT patients (50% vs 23%; p=0.08), while also showing lower relapse rates (0% vs 36; p=0.0013). In non-RVR patients, SVR ratings were higher in CC than CT/TT patients (75% vs 23%; p=0.001). By logistic regression, the IL28B rs12979860 CC genotype was an independent predictor of SVR, with an odds ratio of 11.1 (95% CI, 3.04 to 40.57; p<0.0001) [De Nicola S et al. *Hepatology* 2011].

Looking for Answers in the Extremes: The CHAVI 014 Hemophilia Study

Translation of the genetic architecture of HCV into therapeutic opportunities has been slow [Thurs M et al. *Semin Liver Dis* 2011]. The specific mechanisms of how IL28B polymorphisms affect HCV suppression remain unknown, and how to incorporate current IL28B data into treatment algorithms with pegIFN and RBV is a matter of ongoing debate. However, new technology (eg, whole-genome sequencing) and searches at the extremes of disease transmission might provide new insights and knowledge.

The Center for HIV/AIDS Vaccine Immunology has been looking at a small cohort of hemophiliacs who had been exposed to HIV but remained uninfected despite receiving factor VIII concentrates that were derived from large pools of blood that was collected from donors, some of whom were infected with HIV.

The study, known as CHAV 014, set out to identify any key genetic determinants that might explain the apparent resistance of these exposed seronegatives (ESNs) to HIV. To date, whole-genome sequencing has failed to find any common genetic variants that are associated with HIV resistance among 393 non-HIV infected cases compared with 823 HIV-infected controls.

With the protective genes unlikely to be common ones, the search for much rarer genetic variants that may explain the ESNs' resistance to HIV infection is underway. In the past 2 years, researchers have identified close to 1000 rare variants of interest that might have contributed to protection against HIV acquisition in certain hemophiliacs.

According to Dr. Goldstein, the job now is to confirm genotypes of variants of interest by other techniques, sequence additional ESN and HIV-positive samples, and deep-sequence interesting genes. He concluded that there are sample and phenotype limitations in the study of infectious disease genomics. At the same time, natural variation offers a tremendous resource for leads into vaccine development and treatment.