Editorial

# Risk stratification for Hepatitis B treatment in the molecular age

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Hepatitis B virus (HBV) is a world-wide scourge, affecting over 2 billion individuals, of which an estimated 240 million are chronic carriers of the virus (1). The burden of this disease is in the developing world, particularly in Asia and Africa, where diagnosis and monitoring can be difficult. Once infected, the outcome of the disease is quite variable between individuals, ranging from spontaneous clearance, chronic asymptomatic infection, chronic active infection, to fulminant liver failure (2). Chronically infected individuals are at risk for developing cirrhosis, liver failure and hepatocellular carcinoma (HCC) (15-40% of HBV infected individuals). Importantly, unlike HCC in hepatitis C infected individuals, HCC in HBV infection can occur in non-cirrhotic individuals. Although numerous associations between environmental factors (smoking, alcohol use, male gender), viral factors (viral load, active replication, core and precore mutations) and the development of HCC in chronic HBV infection have been identified, a clear understanding of the role of host genetics remains elusive. Importantly, treatment with direct-acting antiviral medications likely can abrogate much of this risk and prevent these dreaded complications of HBV (3,4). Despite published guidelines regarding the who and when to initiate treatment in HBV infection (5), clinicians anxiously await a better understanding of which individuals with chronic asymptomatic infection will benefit most from these medications.

Treatment with direct acting antiviral medications has long been available for HBV, but none of these treatments are a panacea. Older drugs, such as lamivudine, are associated with significant rates of resistance (3). Newer options, such as tenofovir, are more expensive and have associated toxicities such as renal tubular dysfunction, though the rates of such adverse effects is low and generally reversible with treatment discontinuation. Finally, the burden of disease often lies in regions of the world where the cost of treatment is prohibitive for governments to offer universal treatment. Given all of this, optimal risk stratification for the treatment of HBV remains a goal in both the developing and developed world. Current guidelines base risk stratification on measures of viral load and immune activity, with guidelines targeting individuals with immune active HBV (either HBeAg+ or HBeAg–) for therapy (6). However, individuals with chronic HBV infection in the immune tolerant or inactive carrier phases of HBV infection can progress/revert to the immune active phase. Thus, guidelines recommend screening of these individuals every 3-6 months for evidence of a shift into the immune active phase. With the advent of molecular medicine, we are starting to make headway towards developing predictive algorithms that may identify individuals whose genetics place them at higher risk. Much is known about the environmental risks of tobacco and alcohol use in increasing HCC risk (7). Previous work has also found associations between viral genetic factors and outcome, such as HBV genotype (6), and mutations (8-10). However, even though a large body of literature also exists evaluating the role of host genetics in the development of HCC (6,11-13), the data is scattered and full of noise, underscoring the likely multigenic nature of risk in infected individuals. As we enter the molecular phase of medicine, large banks of data may be able to tease out genetic polymorphisms associated with risk that may help clinicians predict which individuals with the inactive carrier state are at risk for progressing/reverting back into the immune active phase. However, to date, much of this work is based on small samples sizes and is not well validated. The work of Li and colleagues (11) published in the July 2012 issue of PLOS Genetics adds to the previous work of Zhang and colleagues (13), and provides a big step forward for the field.

The manuscript "GWAS Identifies Novel Susceptibility Loci on 6p21.32 and 21q21.3 for Hepatocellular Carcinoma in Chronic Hepatitis B Virus Carriers" describes the extensive work that Li and colleagues used to identify loci associated with hepatocellular carcinoma in chronic HBV carriers (11). The authors used a multistage approach, first using genome-wide association studies (523,663 autosomal SNPs) in 1,538 HBV infected HCC patients and 1,465 chronic HBV carriers all from a Han Chinese population to screen for candidate associations. Thirty-nine candidate SNPs were identified and then evaluated in a validation group that included 2,112 HBV infected HCC patients and 2,208 HBV carriers. This work resulted in validation of 3/39 SNPs, which were then genotyped in a 2$^{nd}$ validation cohort of 1,021 HBV infected HCC patients and 1,491 HBV carriers. This second validation resulted in the confirmation of two of the three previous validated SNPs. Finally, a 4$^{th}$ cohort of 1,298 cases and 1,026 controls was used to evaluate the replicability of these results. The result of this work was the identification of 2 SNPs that had an association with HCC in an HBV infected population. These were rs9272105 on 6p21.32, located between HLA-DQ1 and HLA-DRB1, and rs455804 on 21q21.3, located in the first intron of GRIK1.

HLA-DQ and HLA-DR alleles have both previously been associated with increased risk of HCC (14,15). In this work the authors confirm a relationship between these HLA alleles and HCC, and that the association of rs9272105 with HCC may be more than just an HLA allele association. Interestingly, the authors note that the variant allele of rs9272105 was protective for HBV infection, but was associated with increased risk for the development of HCC. Teleologically this is biologically plausible since a more potent inflammatory response may prevent infection, but once infection is established may lead to the complications associated with chronic inflammation.

GRIK1 encodes a protein involved in glutamate signaling, a pathway known to play an important role in several other tumor types including breast and pancreatic cancer as well as melanoma (11). Therefore polymorphisms in proteins involved in this pathway could have an effect of tumorigenesis.

A potential criticism of the study is the lack of biopsy data or clear descriptions of the various patient cohorts in terms of the degree of underlying liver injury. It would have been very interesting to know whether the association between specific SNPs and HCC is only found in patients with advanced fibrosis or cirrhosis, or if this finding is also seen in inactive carriers with no or minimal fibrosis as well.

If the authors propose that rs9272105 is "protective" in lowering the risk of transitioning to immune active chronic HBV (what the authors termed "symptomatic chronic HBV") from either the immune tolerant or inactive carrier stages of infection (the authors used the term "non-symptomatic chronic HBV"), it may further support the conclusion that the association between this particular SNP and HCC risk may be explained by the risk of developing advanced fibrosis/cirrhosis. From a clinical standpoint, this information could also be very useful to help determine the timing and duration of antiviral therapy in certain populations.

These two associations are just the tip of the iceberg in terms of what has been published in this field. However, very few large-scale GWAS studies addressing this question have been performed. The first of these was published by Zhang *et al*. in 2010 (13) and identified a locus near the KIF1B gene, encoding a protein involved in organelle trafficking. However both Li's and Zhang's studies suffered from finding only weak associations on the initial GWAS, not reaching the commonly accepted association threshold ($P<5\times10^{-7}$) recently defined in a landmark article on GWAS by the Wellcome Trust Case Control Consortium (16). Although subsequent validation and replication cohorts confirmed this association, only the initial P-value is corrected for multiple testing. This issue, along with the finding in other studies that KIF1 was not associated with HCC in non Han Chinese populations (17), underscores the limitations of GWAS studies. Defining the host genetic risk profiles for HCC using these methods will require large sample sizes to address the small effect sizes and the likely multigenic nature of this risk. Additionally, many of these associations may turn out be population specific, due to a confluence of other genetic differences and environmental co-factors, and result in lack of generalizability between populations.

Regardless, the authors should be congratulated on this immense piece of work. Although the field is currently moving small steps at a time, work such as this provides the framework for evaluating genetic associations in relation to clinical outcomes that will be key when the deluge of genomic data begins in the next few years.

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