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Review: Host Genomics and HCV Personalized Medicine

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Abstract. It is estimated that there are 4.0 million individuals chronically infected with Hepatitis C virus (HCV) in the US. Due to the slow progression of disease, the incidence of HCV has declined in the last two decades. However, it is anticipated that the number of individuals requiring treatment for liver disease associated with HCV will increase for years to come. Until 2011, HCV genotype 1 infections were treated with 48 weeks of pegylated interferon and ribavirin combination therapy; only 50% of patients had a successful outcome. Moreover, patients often withdraw from treatment prematurely because of the high cost and adverse effects of therapy. All of these factors make HCV infection a serious healthcare issue.
Recent advances in HCV management include the discovery of host genetic polymorphisms that can predict treatment outcome, as well as the availability of the first direct acting antiviral agents that promise to revolutionize HCV management and increase the likelihood of a favorable treatment outcome. In 2009, multiple independent groups performed genome-wide association studies in HCV infected individuals and identified several single-nucleotide polymorphisms (SNPs) near the IL28B gene that predict the likelihood of both spontaneous and treatment-induced HCV clearance. This article provides an overview of the genome-wide association studies that uncovered the role of the IL28B genotype and reviews the clinical utility of IL28B genotyping.

Hepatitis C Infection. In the United States, the prevalence of HCV infection has been estimated at over 4.0 million cases, of which 80% are suspected to be viremic. Because the immune system has difficulty clearing hepatitis C infection, only 15-30% of individuals who contract HCV clear the virus [1]. The remainder develop chronic hepatitis C infection, which is associated with severe liver disease, including cirrhosis and hepatocellular carcinoma. Chronic HCV infection is currently the primary cause for liver transplantation and also accounts for approximately 10,000 deaths every year [1]. Acute HCV is rarely diagnosed and infected patients often do not have any symptoms until serious complications develop, decades post-infection. This underscores the importance of screening populations that are at increased risk for HCV infection.

Chronic HCV infection can be successfully treated and a virologic cure can be attained, reducing both the long-term complications and the significant rate of mortality and morbidity associated with persistent hepatitis C infection [2]. Successful treatment response for HCV infection is defined as undetectable viremia six months after completion of treatment and is referred to as sustained virologic response (SVR). When treated with pegylated interferon and ribavirin combination therapy, patients infected with HCV genotype 1 infections have substantially lower rates of SVR compared to HCV genotypes 2 and 3, approximately 50% vs. 80% respectively [3]. HCV genotype 1 is the most prevalent genotype in North America, Europe and Japan. HCV genotype is the strongest pre-therapeutic marker for treatment-induced HCV resolution. Measuring the kinetics of viral clearance during therapy to predict the likelihood of SVR is useful for all HCV genotypes. There is a distinct relationship between how rapidly a patient achieves undetectable viremia in response to therapy and the likelihood of attaining SVR. A rapid viral response (RVR), defined as a decrease in HCV viral load to undetectable levels at week 4 of therapy, strongly predicts SVR. Although patients infected

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Table 1. *Summary of GWAS studies for HCV infection outcome.*

Study	Population	HCV Genotype	SNP	Nucleotide	Favorable Genotype
Ge (2009) USA	1671 Americans Caucasian/African-American/Hispanic	1	rs12979860	C/T	CC
Suppiah (2009) Australia	293 Europeans/ Australians	1	rs8099917	T/G	TT
Tanaka (2009) Japan	154 Japanese	1	rs8099917	T/G	TT
Rauch (2010) Switzerland	1362 Caucasians	1,2,3,4	rs8099917	T/G	TT

with HCV genotype 1 are less likely to achieve RVR, its occurrence is the best predictor of SVR. This observation suggested the existence of host factors that affect the likelihood of a positive treatment outcome. In addition to the limited efficacy of treatment, the therapy itself is difficult to tolerate. Individuals can experience serious side effects ranging from psychological depression to bone marrow suppression, often resulting in premature withdrawal from treatment [3]. Given the high cost of treatment, poor response rate for HCV 1, and severe side effects, identifying factors that predict response to therapy would be valuable. However, until the discovery of IL28B SNPs, no host genetic markers were available to predict likelihood of response or drug toxicity prior to therapy.

Genome-wide Association Studies. The human genome consists of approximately 3.3 billion base pairs and is 99.5% identical between individuals. This 0.5% of human genetic variation explains the observed differences between individuals for predisposition to disease, disease course and therapy response. The most common form of genetic variation is sequence difference at a single nucleotide, or single-nucleotide polymorphism (SNP), and there are approximately 10-20 million such differences between individuals. Unraveling the genome and identifying the genetic variation that is responsible for a specific condition, such as treatment-induced clearance of HCV infection, is the essence of personalized medicine.

Genome-wide association studies (GWAS) investigate the genome for genetic variation or SNPs associated with a disease or condition of interest by utilizing high throughput technologies. If an SNP is overrepresented in the affected population vs. in the control population, then the SNP is associated with the condition of interest. SNPs vary in a nonrandom manner within a chromosomal region and although SNPs may be distantly located on a chromosome, they can be inherited together as a block or haplotype and are said to be in linkage disequilibrium [4]. It is therefore possible for researchers to scan the genome with only a limited number of "tag" SNPs (e.g. 500,000-2,000,000) and still detect polymorphisms associated with a phenotype. However, this strategy rarely identifies the causal variant associated with an observed effect. The causal variant SNP and the tag SNP are usually in varying degrees of linkage disequilibrium. The "tag" SNP generally marks a chromosomal region of interest but not a specific gene. The location and distribution of common SNPs and haplotypes is made possible by the HapMap project [5, 6].

Compared to the traditional gene candidate approach, this strategy can identify functionally important polymorphisms in genes that have an unexpected role in disease pathogenesis. Results of GWAS are dependent on appropriate selection of control and affected populations, large sample cohorts, and adequate statistical analysis for use with large data sets. In general, GWAS are successful when the association is strong and/or when the variant is relatively common, but these conditions are frequently not met [7, 8].

IL28B genotype and HCV clearance. The role of the IL28B genotype in predicting the likelihood of a positive outcome response was largely discovered using genome-wide association studies (GWAS). Using various microarray technologies, several independent groups from the US, Australia, Europe, and Japan identified a series of SNPs associated with treatment outcome in populations of different ethnic backgrounds infected with various HCV genotypes **(Table 1)**. Ge and colleagues conducted a genome-wide association study with US patients enrolled in the IDEAL trial that evaluated different pegylated interferon/ribavirin formulations. The patient cohort consisted of over 1,600 patients of different ethnic backgrounds, including Caucasians, African-Americans, and Hispanics [9]. Data demonstrated that patients with the rs12979860 CC genotype were twice as likely to achieve SVR than were CT-heterozygous or TT-homozygous individuals. This effect was observed regardless of ethnic background. Even African-Americans carrying the CC genotype were likely to achieve SVR, an exciting finding as it is well known that African-Americans are less likely to be cured by treatment than are Caucasians. The IL28B genotype only partially explains the differential therapy response rates between African-Americans and Caucasians [9, 10].

Tanaka's group used the Affymetrix genotyping platform to test the non-responder phenotype in a Japanese cohort and identified the rs8099917 SNP as the strongest predictor of non-response, independent of other clinical variables [11]. For the rs8099917 T/G SNP, T is the favorable and G the risk allele. The Affymetrix microarray did not include the rs12979860 tag SNP discovered by Ge. Suppiah assessed an Australian patient cohort and regression analysis further confirmed the IL28B genotype as an independent predictor of significant SVR rates [12].

The IL28B genotype has also been implicated in spontaneous HCV clearance. Ge first reported that the CC favorable genotype was present at a reduced frequency in the control population compared to the HCV infected cohort, suggesting that the IL28B genotype also played a critical role in spontaneous clearance. Thomas specifically addressed the association of the IL28B with spontaneous clearance using an ethnically diverse population composed of six clinical trial cohorts and found that the CC genotype for rs12979860 was present 2.5 times more frequently in patients that resolved HCV infection in the absence of treatment [10]. To gain insight into the variable HCV resolution rates observed across different ethnic groups, the investigators genotyped 2,371 persons from 51 populations worldwide and determined the global distribution of the rs12979860 alleles. The protective C allele dominated in Asia, was of intermediate frequency in Europe, and was rare in Africa. The data were consistent with the differential rates of HCV clearance noted globally. The Rauch group assessed 347 patients who spontaneously cleared HCV, 1062 patients with persistent HCV infection (HCV genotypes 1-4), and 448 HIV/HCV coinfected persons. Both chronic hepatitis C infection and treatment failure were associated with the risk allele for rs8099917. The IL28B genotype effect was strongest in individuals infected with HCV genotypes 1 and 4. The IL28B genotype predicted spontaneous clearance, but HIV coinfection did not modulate the effects of the IL28B genotype [13].

Initial GWAS identified SNPs associated with HCV clearance. Subsequent studies addressed the significance and predictive power of the SNPs. McCarthy and colleagues conducted a candidate gene approach and determined that the rs12979860 CC genotype predicted SVR in Caucasians independently of other covariates, including HCV genotype [14]. Studies by Thompson and colleagues further investigated the clinical utility of the IL28B genotype in patients infected with HCV genotype 1 and concluded that the IL28B genotype is the strongest pre-treatment predictor compared

to previously described host markers including gender, age, steatosis, insulin resistance, and baseline viral load. However, rapid viral response (RVR) remains the strongest predictor of SVR, irrespective of IL28B genotype. In the group that did not achieve RVR, patients with the favorable rs12979860 CC genotype were twice as likely to attain SVR compared to non-CC genotypes [15]. In Caucasians infected with HCV genotype 1 and treated with standard of care therapy (pegylated interferon and ribavirin therapy), SVR rates were 69%, 33%, and 27% for CC, CT, and TT genotypes, respectively. For African-Americans, SVR rates were 48%, 15% and 13% , for CC, CT and TT genotypes, respectively [15]. Altogether, numerous studies have provided indisputable support for the role of the IL28B genotype as a predictor of both spontaneous and treatment-induced HCV clearance.

IL28B and HIV/HCV coinfections. Approximately one-third of HIV-positive individuals are coinfected with HCV. Many studies have confirmed that the IL28B genotype is a significant and independent predictor of SVR and spontaneous clearance in this population as well [10, 13, 16-18]. As is the case with HCV mono-infected populations the strongest effect is with HCV genotypes 1 and 4 [10, 13]. Although favorable IL28B genotype is associated with a positive HCV treatment outcome, one group recently reported that the IL28B genotype is associated with increased mortality in coinfected populations [19]. More data are needed before specific recommendations can be made for the treatment of HIV/HCV coinfected individuals.

IL28B and transplantation. Not only is HCV infection the leading cause of liver transplants, HCV recurrence is also almost guaranteed in patients who are viremic at the time of transplantation. Treatment in the post-transplant setting is complicated by drug-drug interactions, risk of toxicity, and transplant rejection. In general, achieving SVR is a challenge. Therefore, numerous researchers have recently investigated the role of the IL28 genotype in predicting liver transplant success. Published reports suggest that: 1) the favorable IL28B genotype is less frequent in HCV patients who have severe liver disease and need a transplant; 2) both donor and recipient IL28B genotype have an effect on the likelihood of achieving SVR in a post-transplant setting; 3) the association between the IL28B genotype and other liver transplant outcomes is not as clear [20-25]. More definitive studies are necessary before IL28 genotype information in the setting of post-liver transplant can be integrated into clinical practice.

IL28B and direct-acting antiviral agents. The discovery that host genetic variation is associated with significant SVR rates is only one of the important developments in HCV management that have occurred in the last two years. The other major advance is the introduction of the first class of drugs that specifically target HCV, are referred to as direct-acting antiviral agents (DAAs). The first DAAs to be cleared by the FDA for use in the US, Telaprevir and Boceprevir, are both NS3/4A serine protease inhibitors. The significance of the IL28B genotype was originally discovered in patients infected with HCV who were undergoing standard of care treatment (pegylated interferon and ribavarin). The addition of a protease inhibitor to SOC, referred to as triple therapy, has been shown to significantly increase SVR rates to 80% in HCV genotype 1 infected patients, but has called into question the relevance of IL28B polymorphisms [26, 27]. Triple therapy is now the optimal treatment regimen for HCV genotype 1 patients [28]. The IL28B genotype remains predictive of SVR in persons being treated with triple therapy [29, 30]. Because higher SVR rates are observed in HCV genotype 1 patients on triple therapy compared to those on SOC, guidelines do not recommend one therapy over another based on IL28 genotype [28]. However, patients with a favorable IL28B genotype are more likely to have abbreviated therapy under triple therapy regimens [29-31].

IL28B mechanism. The mechanism by which the IL28B genotype exerts its effects is the target of intense investigation. All SNPs that had a strong association with HCV clearance mapped to the region of IL28A, IL28B, and IL29 interleukin genes on chromosome 19q13. These genes encode a

recently discovered family of interferons known as type III or lambda interferons. Lambda interferons have been shown to inhibit HCV in vitro and are believed to trigger an anti-viral cascade through the JAK-STAT pathway [32, 33]. The two SNPs with the strongest association for treatment response, rs12979860 and rs8099917, are in linkage disequilibrium, approximately 4 kb apart, and are both located upstream of IL28B. The upstream location of IL28B prompted investigators to postulate that the causal variant affects gene transcription. Expression studies, however, have yielded mixed results. While the biological mechanism behind the IL28B genotype remains to be determined, the overwhelming evidence indicates that it is a critical and independent factor in HCV clearance.

IL28B genotype in clinical practice. Today, commonly utilized genotyping technologies such as TaqMan allelic discrimination and dual-color fluorescence resonance energy (FRET) are commercially available for IL28B genotyping [34]. Ultimately, two SNPs (rs12979860 and rs8099917) were shown to have the strongest association with both spontaneous and treatment-induced HCV clearance and became candidates for IL28B genotype assays. While these two SNPs are in linkage disequilibrium, the degree of linkage disequilibrium varies with ethnic background [9, 13, 34, 35]. These data indicate that the two SNPs provide interchangeable information in Caucasians, for example, but not in populations with weak linkage, such as African-Americans. In multiple studies, the rs12979860 CC favorable genotype was clearly associated with a significant rate of SVR in African-Americans [9, 10]. Few studies have genotyped for both SNPs and evaluated HCV clearance. Although there are limited data that suggest the rs12979860 may be the more relevant SNP, in patients who are discordant for these two SNPs it is not well established which of the two SNPs is more reflective of observed response.

In summary, IL28B genotyping is a strong pre-treatment predictor of SVR in patients with HCV genotype 1 infections irrespective of treatment regimen (SOC or triple therapy). Predictive value is lower in patients infected with HCV genotypes 2 and 3 [13, 28, 36]. Therapy (SOC or triple therapy) selection and duration for HCV genotype 1 infections should not be based on IL28 status. According to current guidelines, the IL28B genotype should be considered if information regarding the likelihood of a positive response and probable duration of response is useful for the clinician and patient [28]. Most importantly, not all patients with a favorable IL28B genotype are guaranteed to have a successful therapy outcome and conversely, not all patients with a risk genotype are destined to fail therapy.

Conclusion

It had long been suspected that host genetics contributed to an individual's ability to clear HCV infection, but it was gene-wide association studies which first identified the IL28B genotype as a powerful predictor for both spontaneous and treatment-induced clearance. Currently, the IL28B genotype has limited clinical use and serves primarily as a strong pre-treatment predictor, most useful for HCV genotype 1 infected patients undergoing either standard of care or triple therapy treatment regimens. The IL28B genotype may play a more active role in patient management in the future, with the integration of other therapeutic agents that target a myriad of processes in the viral lifecycle; these pharmaceuticals are in various stages of clinical trials. Cost-benefit analysis based on successful response to a growing number of therapeutic options and IL28B genotype may also alter future recommendations for the clinical use of the IL28B genotype.

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