REVIEW

IL28B Genomic-Based Treatment Paradigms for Patients With Chronic Hepatitis C Infection: The Future of Personalized HCV Therapies

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Genome-wide association studies (GWAS) have recently identified host genetic variation to be critical for predicting treatment response and spontaneous clearance in patients infected with hepatitis C virus (HCV). These important new studies are reviewed and their future clinical implications discussed. Single-nucleotide polymorphisms in the region of the *IL28B* gene on chromosome 19, coding for the interferon (IFN)-λ-3 or *IL28B* gene, are strongly associated with treatment response to pegylated IFN and ribavirin in patients infected with genotype 1 HCV. The good response variant is associated with a twofold increase in the rate of cure. Allele frequencies differ between ethnic groups, largely explaining the observed differences in response rates between Caucasians, African Americans and Asians. *IL28B* polymorphism is also strongly associated with spontaneous clearance of HCV. The biological mechanisms responsible for these genetic associations remain unknown and are the focus of ongoing research. Knowledge of a patient's *IL28B* genotype is likely to aid in clinical decision making with standard of care regimens. Future studies will investigate the possibility of individualizing treatment duration and novel regimens according to *IL28B* type.

Am J Gastroenterol 2011; 106:38–45; doi:10.1038/ajg.2010.370; published online 5 October 2010

INTRODUCTION

The unraveling of the human genome offers the promise of personalized medicine. In this review, we briefly define some critical genetic concepts for clinicians, and overview genome-wide association studies (GWAS). Readers are directed to excellent genetics reviews for further reading (1–3). We review the recent GWAS discovery, which has shown that host genetics drives treatment response to pegylated interferon-α and ribavirin (pegIFN/RIB) for patients infected with genotype 1 hepatitis C virus (HCV) (4–6). We also review recent studies that have shown that the same polymorphisms are associated with spontaneous clearance of HCV (7,8).

HUMAN GENETIC VARIATION AND EXAMINING CLINICAL ASSOCIATIONS

The human genome contains over 3.3 billion base pairs. In excess of 10 million of these may vary in nucleotide sequence between individuals (single-nucleotide polymorphism or SNP). Some of this variation may result in altered expression of the gene, altered processing of the gene product (post-translational modification), or altered functional activity (e.g., receptor binding). Identifying polymorphisms that result in altered clinical expression (phenotype) is a daunting challenge, analogous to finding a "needle in a haystack" (1).

SNPs vary within a region of a chromosome (or haplotype block) in a nonrandom way. Across populations, nonrandom association of SNPs is referred to as linkage disequilibrium (9). Because of linkage disequilibrium, researchers can sample a limited number of SNPs (tag SNPs) but assess common variation across approximately 90% of the genome (10). Using microarray technology on commercialized chips or beads more than 1 million tag SNPs can now be tested in any individual DNA sample (**Figure 1**).

These common SNPs are available due to the efforts of the HapMap project (11), which is a public database of "hotspots" of common haplotypes (occurring in >5% of the population). Therefore, an important caveat for GWAS is that rarer variants (occurring in <5% of the population) may not be identified.

The goal of an initial study is to "flag" or identify genetic areas of interest. The causal genetic variant responsible for disease is rarely identified. GWAS therefore use *genetic sampling technology* and *bioinformatics* to *statistically test* for association of *genotype* with a clearly defined *phenotype* without limiting the sample by a predetermined hypothesis (**Figure 2**).

From the above, GWAS results rely on the size of the cohort; technical issues related to testing platforms and quality control; and how extensively the genome is sampled (how many SNPs are tested per individual). Increasingly, powerful testing platforms also raise new problems that arise from handling large data sets. The

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Received 5 April 2010; accepted 16 August 2010

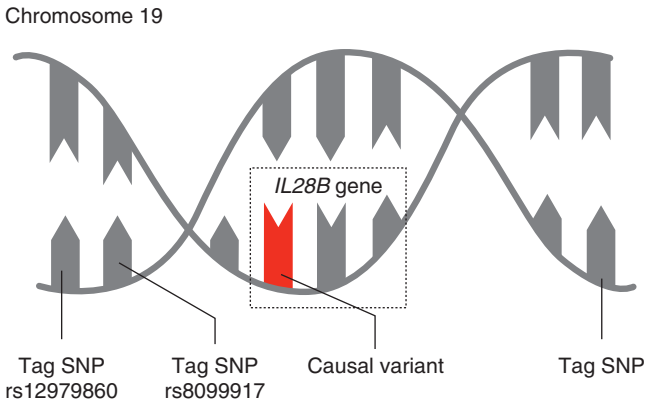

Figure 1. The principle of tag single-nucleotide polymorphism (SNP) sampling. Tag SNPs (shown in gray) are used as markers to sample a haplotype block. The tag SNP is representative of the common variants within this block, which are associated through linkage disequilibrium. The causal variant (shown in red) is rarely identified. In this study, we show schematically the IL28B gene on chromosome 19 relevant to hepatitis C. Tag SNPs are used on commercially available SNPchips—hundreds of thousands of of tag SNPs on a chip are used to capture the variation of the more than 10,000,000 common variants recognized on the human genome. There can be multiple tag SNPs associated with a gene as shown, which are often kilobases apart, rather than adjacent nucleotides as indicated in the figure.

ability to test millions of SNPs per individual leads to the challenge of multiple testing (i.e., if the chance of a false-positive test is 0.05, then a million SNP chip will identify 50,000 false-positive associations) and requires statistical measures such as the Bonferroni correction to avoid false-positive results (Type 1 error). Finally, well-characterized clinical cohorts with clearly defined phenotypes are critical to avoid spurious results and genetic associations.

Early genetic association studies have in many cases not been reproducible (12–15), likely due to such problems as restricted genetic sampling on small cohorts often using the candidate gene approach; indistinct phenotypic characterization and statistical methodological problems (2,16). Improvements in high throughput DNA microarray technology have moderated the prohibitive cost and time previously involved with extensive sampling of large cohorts. For example, a chip containing 500,000–1 million SNPs now only costs approximately US$390–500. Evolving consensus on what characterizes genetic probability and statistical significance has allowed some degree of standardization of results and interpretation of GWAS (17–19).

GENOMIC VARIATION AND HEPATITIS C

The problem

Current treatment for patients chronically infected with genotype 1 HCV requires 48 weeks of pegIFN/RBV. The goal of treatment is viral eradication (sustained viral response (SVR) defined as the absence of virus 24 weeks after treatment completion), but this is achieved in <50% of patients (20,21).

Therapy is also frequently complicated by treatment-limiting side effects (22). An accurate ability to predict response would

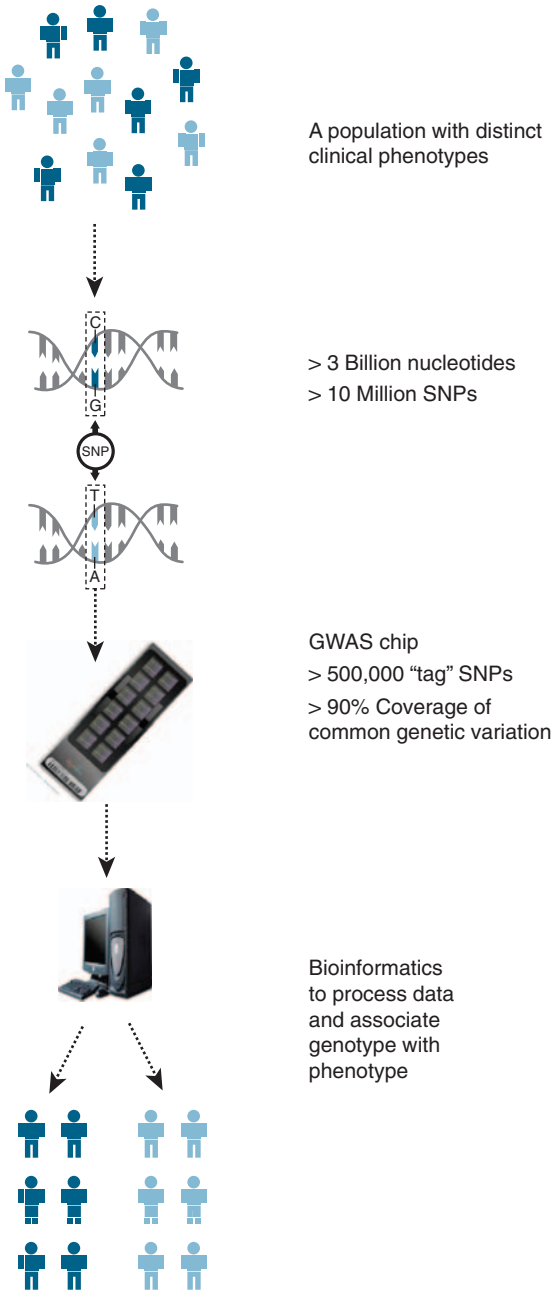

Figure 2. The principle of genome-wide association studies (GWAS). A population with distinct clinical phenotypes (as shown) is hypothesized to contain a genetic marker. The human genome contains more than 3 billion nucleotides with over 10 million single-nucleotide polymorphisms (SNPs). Genetic polymorphism is assessed using microarray chips or beads (shown) generating massive amounts of information. Each chip contains hundreds of thousands of tag SNPs, which cover more than 90% of common genetic variation. Powerful bioinformatics platforms are then applied to this information and correlated with the well-defined clinical phenotype.

allow both patients and clinicians to make more informed decisions regarding the risk-benefit of treatment, and the likelihood of success for any given individual.

Based on population data, several key host and viral factors aid in predicting response to this treatment. Host factors that have been

negatively reported to affect likelihood of SVR include age >40 years, advanced degrees of liver fibrosis, male gender, increased body mass index, insulin resistance, and hepatic steatosis (23–25). In addition, African-American patients are less likely to respond to treatment, an observation independent of other host and viral factors (26–28). Viral factors predictive of non-response response include genotype 1, lack of diversity in key genetic sequences, especially amino-acid mutations in the core and NS5A gene (29,30), high pretreatment HCV RNA levels, and on-treatment viral kinetics (31). Week 4 viral negativity (rapid viral response (RVR)) accurately predicts SVR, whereas failure to reduce serum HCV RNA levels by at least 2 $\log_{10}$ IU/ml by week 12 (early viral response) predicts treatment failure and is considered to be an indication to cease therapy (32). The fact that only 50% of patients are cured by treatment and the influence of ethnicity on response both suggest a genetic contribution to HCV treatment outcome.

Host *IL28B* genotype and SVR

Recent GWAS have identified SNPs around the gene coding for IFN-λ-3 (or *IL28B*), associated with favorable response to treatment in patients infected with genotype 1 HCV (4–6).

Patients in the first and largest GWAS were enrolled in the IDEAL trial, a randomized control trial comparing different doses of pegIFNα-2b/RBV with peg-IFNα-2a/RBV (21). DNA from a further 67 similarly well-characterized patients in a second randomized controlled trial analyzing racial differences in treatment response were also included (27). To clearly define the biological response phenotype, non-responders were excluded if they were not documented to be adherent and received at least 80% of the prescribed dose.

Overall, 1,137 patients were included in the genetic association analyses for SVR in three separate ethnic populations, defined by genetic ancestry (Caucasian, Hispanic, and African American (AA)). Seven SNPs were identified that overwhelmingly met genome-wide significance with the top discovery SNP (rs12979860) strongly associated with SVR ($P = 1.37 \times 10^{-28}$). A number of other SNPs (including rs8099917 associated in other studies) were also significantly associated, but highly correlated with the discovery SNP due to linkage disequilibrium. Regression modeling found that the *IL28B* polymorphism (rs12979860) was the strongest predictor of SVR compared with all other baseline host and viral variables (**Figure 3**).

An intention-to-treat analysis was performed that included all patients, regardless of adherence, and classifying ethnicity by self-report as it would be in practice. Again, the good response variant (C/C, patients with two copies of the C allele at the discovery SNP rs12979860) was associated with a two- to threefold increase in SVR rate in the three ethnic groups (33).

RVR remains a critical predictor of eventual SVR irrespective of host *IL28B* genotype. Importantly, in those patients who *fail* to achieve RVR, SVR rates were more than twofold higher in *IL28B* C/C patients compared with patients with unfavorable non-C/C genotype (33). This suggests that host *IL28B* genotype will add further predictive power for patients who fail to meet existing criteria currently used to predict response.

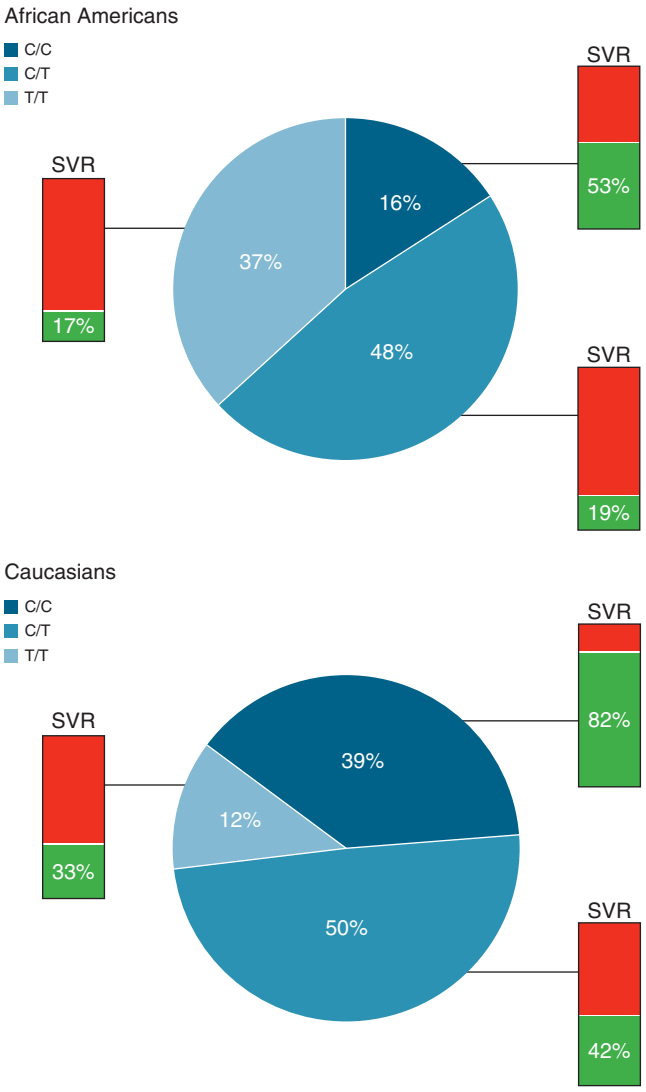

Figure 3. Sustained virological response (SVR) rates by host *IL28B* genotype for African Americans (above) and Caucasians (below) (Ge *et al.* (4)) (1). Note that these data are from an adherent cohort. For each ethnic group, the proportion of patients with favorable *IL28B* C/C, and the C/T and T/T less favorable genotypes is shown in the central blue chart. For each of these groups, the SVR rates are depicted in the corresponding bar charts. The percentage SVR rate is shown in green. As can be seen, those patients with the *IL28B* C/C genotype have the highest SVR rates.

Other GWAS have independently identified the IL28B region to be an important predictor of SVR. Tanaka *et al.* (6) tested an initial GWAS discovery cohort of 142 patients followed by a replication study of a further 172 patients, all of Japanese ethnicity. They tested the clinical phenotype of non-response (<2 log reduction in HCV RNA at 12 weeks of treatment). Patients who received <80% of therapy up to week 12 were also excluded. Two SNPs (rs8099917 and rs12980275) near the *IL28B* gene were identified to be strongly associated with non-response. Modeling revealed rs8099917 to be the strongest predictor of non-response, independent of other clinical variables. Tanaka *et al.* (6) used an Affymetrix 6.0 genotyping platform, which did not include

rs12979860 (the top SNP from the Ge *et al.* (4) study) as a tag SNP on the array.

Suppiah *et al.* (5) employed a similar two stage GWAS process to Tanaka *et al.* (6). A discovery cohort of well-matched Australian patients ($n=293$) of European ancestry was assessed in the initial GWAS and one SNP (rs8099917, $P=7.06\times10^{-8}$) met the criteria for statistical significance. In the second replication study, Suppiah *et al.* (5) assessed a population of European and Australian patients ($n=555$) and further confirmed the association of rs8099917 with SVR (combined cohort $P=9.25\times10^{-9}$). Regression analysis again confirmed rs8099917 to be an independent predictor of response ($P<0.0001$).

Two more recently published studies have replicated these findings. In a large GWAS on a heterogeneous group of patients, Rauch *et al.* (8) identified the *IL28B* gene region (rs8099917) to be to be independently associated with treatment failure (odds ratio (OR) 5.19 (2.90–9.30), $P=3.11\times10^{-8}$). The study also assessed spontaneous clearance and the effect of host genotype on HCV/HIV coinfection (discussed below). McCarthy *et al.* (34) investigated the association with host *IL28B* genotype (rs12979360) and SVR in a cohort of 231 clinic patients. This study again confirmed the *IL28B* CC genotype to be the strongest pretreatment predictor of response, independent of other pretreatment clinical predictors and HCV genotype (OR 5.79 (2.76–12.57) $P=9.0\times10^{-6}$).

In summary, a number of SNPs around the *IL28B* gene locus were found across the studies to be associated with treatment response. All displayed at least moderate linkage disequilibrium. The characteristics of each study (e.g., population racial distribution, sample sizes, and clinical phenotype assessed) and the SNPs represented on the different chips obviously influence the nature and significance of results and are likely to explain the discrepancy in top SNPs found. An important conclusion is that all these studies implicate the *IL28B* gene as a predictor of treatment response.

Host *IL28B* genotype, ethnicity, and the effect on SVR

Differences between ethnicity and treatment response rates are poorly explained by host clinical factors or compliance, suggesting a key role for host genetics (26,27). The *IL28B* polymorphism rs12979860 has a marked differential distribution between racial groups, being least frequent in AAs, most frequent in Asians, and with an intermediate frequency in Hispanics and Caucasians (4,7) (**Figure 3**).

In the study by Ge *et al.* (4), *IL28B* genotype variation statistically explained approximately half of the observed difference in SVR rate between Caucasians and AA (4). However, it did not entirely explain the difference, and AAs still had poorer response rates across each host *IL28B* genotype than Caucasians. It is therefore possible that there are other genetic factors that may contribute to IFN sensitivity, particularly in AA patients.

Host *IL28B* genotype and spontaneous clearance

Spontaneous clearance of HCV occurs in approximately 20–50% of patients following acute infection, and host genetics has been previously suggested to have a significant role (35–38). In the same GWAS related to treatment response, Ge *et al.* (4) found the rs12979860 C allele significantly more common in a random multiethnic population compared with an HCV-infected control cohort ($P=2.48\times10^{-6}$) (4). This raised the question of whether the C allele affords some protection against the development of chronic HCV infection.

Thomas *et al.* (7) subsequently evaluated the SNP rs12979860 to assess the association with spontaneous clearance. They investigated an ethnically diverse population of 1,008 individuals from six different clinical and study cohorts, with either spontaneous clearance of acute HCV infection or the development of persistent infection. Across all cohorts, those with the C/C genotype were three times more likely to clear HCV acutely relative to non-C/C (i.e., heterozygotes (C/T), and homozygotes for the minor allele (T/T) (OR 0.33; $P<10^{-12}$). Thomas *et al.* (7) found that polymorphism at the *IL28B* gene demonstrates a similar effect on spontaneous clearance across ethnic groups.

In line with this observation, Rauch *et al.* (8) conducted a GWAS on a Caucasian cohort of 347 patients who had spontaneously cleared HCV and compared them to 1,015 patients with chronic hepatitis C. They extended previous studies by finding that only the *IL28B* gene locus was associated with clearance (OR 2.31 (1.74–3.06), $P=6.07\times10^{-9}$), with some minor advantage conferred to heterozygotes.

Other emerging *IL28B* data

The introduction of direct acting antivirals (DAAV) (or specifically targeted antiviral therapies) is the most important recent therapeutic advance for patients infected with HCV and will lead to significantly improved overall SVR rates (39,40). Akuta *et al.* (41) recently assessed a cohort of Japanese patients infected with genotype 1b HCV and high viral load treated with either 12 weeks of telaprevir/peg-IFN/RBV ($n=20$) or 12 weeks of triple therapy followed by a further 12 weeks of peg-IFN/RBV ($n=61$). They found that *IL28B* polymorphism (rs8099917) remained the strongest pretreatment predictor of response, despite the addition of telaprevir. Interestingly, the majority of these patients were either non-responders or relapsers to prior treatment, suggesting that *IL28B* may exert effect in this specific patient population and be an important consideration in retreatment studies.

Akuta *et al.* (41) also directly sequenced the virus for amino-acid substitutions in the core and NS5A-IFN sensitivity determining regions. In multivariable analysis, patients who were heterozygous or homozygous for the poor response *IL28B* polymorphism were more likely to achieve SVR in the setting of amino-acid substitution Arg70 rather than Gln70(His70) (50 vs. 11.8%, $P=0.038$). More data are required from other ethnic groups and from larger treatment naïve cohorts to assess what residual role viral amino-acid substitutions have in pretreatment prediction of response to DAAV inclusive regimens.

Further data concerning the relevance of *IL28B* polymorphism in non-genotype-1 HCV infection is emerging. Analysis of an Italian genotype 2 and 3 cohort ($n=268$) found IL28B to be associated with SVR and a significant variable in a predictive model (42). Rauch *et al.* (8) found no significant impact of host *IL28B*

genotype on treatment response in HCV genotype 2/3 patients when comparing 230 patients with HCV genotype 2 or 3 with a matched group of 232 patients with HCV genotype 1 or 4. These findings were also observed in patients coinfected with HIV and HCV genotype 3 by Rallón *et al.* (43). *IL28B* polymorphisms may be important for subgroups of genotype 2/3 patients, where C/C genotype patients who failed to achieve RVR were more likely to achieve SVR than non-C/C genotype (42). Non-genotype 1 infection is generally more successfully treated, thus limiting the advantage conferred from favorable *IL28B* polymorphism, and requires a better-powered cohort to find statistically significant associations.

IL28B genotype appears to be important in the setting of HIV/HCV coinfection. Rallón *et al.* (43) found a strong association between host *IL28B* genotype and treatment response in a cohort of 164 treated HIV/HCV coinfected patients, with SVR rates of 75% for patients with the C/C allele compared with 38% for those with the C/T or T/T allele ($P = < 0.0001$). Nattermann *et al.* (44) studied another HIV/HCV patient cohort and in univariable analysis found SVR rates of 58.1 vs. 40.6% for responder and non-responder genotypes, respectively ($P = 0.041$). Rauch *et al.* (8) assessed the association between spontaneous clearance and host genotype with GWAS in 448 patients coinfected with HIV/HCV and found a similar signal for *IL28B* to that found in monoinfected patients (OR 2.16 (1.47–3.18), $P = 8.24 \times 10^{-5}$ vs. OR 2.49 (1.64–3.79), $P = 1.96 \times 10^{-5}$, respectively), a finding consistent with Thomas *et al.* (7,8).

Clearly, more data related to DAAVs, different HCV genotypes, treatment response, and the effect of *IL28B* genotype in the post-transplant setting and in other treatment regimens with novel agents are eagerly awaited.

How is *IL28B* polymorphism biologically associated with these clinical observations?

Although the identified SNPs may not represent causal variants, the strong association replicated on multiple occasions now implicates the *IL28B* gene and IFN-λ as the "smoking gun" for response and clearance. However, the biological pathways underpinning this association remain unknown.

The top association SNPs lie upstream of the *IL28B* gene and it is therefore possible that they effect *IL28B* transcription. Ge *et al.* (4) observed no relationship between *IL28B* mRNA levels and *IL28B* polymorphism in peripheral blood mononuclear cells from non-HCV-infected volunteers in the SNPExpress database (using genotype at rs12980275 as a proxy for rs12979860 genotype, $r^2 = 0.88$) (4). Tanaka *et al. et al.* (6) measured *IL28B* mRNA from the peripheral blood mononuclear cells in a small subgroup of 20 patients (6). Using quantitative real-time PCR, they found that rs80999917 poor-responder allele homozygotes had lower levels of *IL28B* mRNA expression. In a limited sample of patients not infected with HCV, Suppiah *et al.* (5) found lower constitutive expression of *IL28A* and *IL28B* in patients with the rs8099917 poor-responder allele ($P = 0.044$). The data on gene expression are therefore conflicting and further studies will be required. Several other potentially functional SNPs have been identified. These include a non-synonymous SNP (rs8103142) in exon 2 of the gene (4). This polymorphism might potentially affect protein function, including receptor binding, or protein stability. Because of the high degree of linkage disequilibrium between these variants, it has not been possible to statistically determine which SNP was responsible for the association signal (the causal variant).

Type III IFNs (or IFN-λ) share many characteristics with the Type I IFNs. IFN-λ (including *IL28A*, *IL28B*, and *IL29*) signals via a unique receptor, the IFN- λR, which has a more liver-specific distribution than the ubiquitous type I IFN-R (45). The receptors share a common downstream signaling pathway, via the Janus-activated kinases–signal transducer and activator of transcriptions 1 and 2 (JAK–STAT) pathway. This leads to intranuclear activation of the IFN-stimulated response element and IFN-stimulated genes (46,47). IFN-λ1/2 have been shown *in vitro* to have antiviral activity against HCV; although less potent than IFN-α, it appears to have an additive or synergistic effect in combination (48,49). IFN-λ1 (*IL29*) has also recently been shown to have potent antiviral activity in a phase 1 study of patients with genotype 1 chronic hepatitis C, although there is no data as yet on whether host *IL28B* genotype is relevant to its the therapeutic effect (50).

How is *IL28B* polymorphism linked to improved treatment induced and spontaneous clearance? At this stage the answer remains unknown, although hypotheses proliferate. It would seem reasonable that as a starting point, *IL28B* polymorphism may affect the IFN-λ system. The complexity of interaction between HCV and the host immune system, and the redundancy within innate and cell-mediated immune systems suggests that this effect will likely be iterative and multileveled. Although the mechanism underlying the association between *IL28B* polymorphism and HCV treatment response/spontaneous clearance is yet to be resolved, the observation has great biological plausibility, and identifies the IFN-λ axis as an important new area for translational research.

What do these findings mean for clinicians managing patients with chronic hepatitis C?

A commercial test is now available for *IL28B*, but how should this information be used to improve care for patients? Patients may be "profiled" based on *IL28B* genotype and other important clinical features (such as fibrosis, age, insulin resistance, viral load, and race) to better predict treatment response (**Table 1**). Host *IL28B* genotype is the strongest *pretreatment* predictor of response through its effect on viral kinetics (33). On-treatment viral kinetics (currently RVR or early viral response, but potentially even earlier measures) provides direct measurement of treatment response and remains the most powerful *on-treatment* response predictor and the key criteria for on-treatment therapy decisions. Importantly, host genotype also adds to current response-guided decision algorithms. The *IL28B* CC genotype identifies a subgroup of patients without RVR who are more likely to achieve SVR. When new DAAV agents in development become available, such profiles may also help both in the choice of treatment regimen and its anticipated duration, personalizing therapy further.

Clinical message: Patient profiles which integrate IL28B genotype and other important clinical variables will be used to help predict

Table 1. Host *IL28B* genotype and other important patient characteristics will be used to develop patient profiles to help predict response and potentially tailor therapy

Host *IL28B* genotype (rs12979860)		
T/T	**C/T**	**C/C**
Other important pretreatment factors		
Genotype 1	Viral genotype	Genotypes 2 and 3
>600,000	Viral load (IU/ml)	<600,000
African American (AA)	Race	Non-AA
F3 and F4	Fibrosis (METAVIR grade)	F0 and F1
Male	Gender	Female
>40	Age (years)	<40
Less likely to respond	⟷	More likely to respond

response and personalize therapy before commencement. As the number of therapeutic options expands in coming years, this may help to simplify and optimize treatment algorithms.

Clinical message: Patients with genotype 1 who do not achieve RVR but carry favorable IL28B type have a 65% chance of cure.

Current standard of care therapy with pegIFN/RBV provides excellent results in patients with genotype 1 HCV and the favorable host *IL28B* genotype. At the bedside, knowledge of this host genotype will translate into greater confidence in terms of counseling patients before commencing treatment. Discussions with a patient about an 80% likelihood of treatment response versus a 30% response rate are very different conversations and akin to discussions we currently have with patients about the impact of ethnicity or viral genotype on predicted treatment response. When on treatment, host *IL28B* genotype knowledge may assist clinicians and patients to "stay the course" when troubled by side effects that may or may not require dose reductions, by the knowledge they have more than simply a "50/50" chance of success in favorable responder genotype patients.

Clinical message: Patients with a favorable patient profile (e.g., C/C IL28B genotype) are likely to respond to current standard of care therapy. This knowledge changes the "cost/benefit" of treatment and may help to encourage patients to commence treatment and to reassure them during a long and often difficult treatment course.

PegIFN/RBV therapy alone avoids the selection for point-specific HCV mutations that may lead to drug resistance when treating with DAAV agents. Existing treatment regimens also avoid exposure to the potential of further drug side effects and toxicity that may be observed with new agents. Finally, existing combination therapy may prove more cost-effective in those most likely to respond, relative to simply adding DAAV onto existing regimens.

Clinical message: Although current standard of care therapy has its drawbacks, for patients with a high likelihood of response (e.g., C/C genotype) it avoids many of the additional problems and costs of future pegIFN/RBV + DAAV combination regimens.

On the basis of available data, patients with unfavorable responder genotype should probably be categorized as "difficult to treat" in the same way clinicians consider other negative treatment prognostic criteria (e.g., advanced fibrosis). It seems likely that the addition of directly acting antiviral therapy may attenuate the effect of host *IL28B* genotype on SVR; however, further studies are needed (40,41). For patients who have the unfavorable *IL28B* genotype, it may be prudent to defer treatment until future regimens that include directly acting antiviral agents become available in 2011–12.

Clinical message: Patients with an unfavorable response profile (e.g., non-C/C genotype) are most likely to benefit from improved SVR rates with regimens that include DAAVs, and they should probably wait for such therapies.

How knowledge of a patient's *IL28B* genotype will alter treatment algorithms is unknown. Patients with the favorable *IL28B* C/C genotype may achieve adequate SVR rates with a reduced duration of current standard of care (e.g., 24 weeks or less compared with the current 48 weeks). Alternatively, in C/C genotype patients the addition of DAAV therapy may provide a pathway to even further reduce the duration of treatment. For patients with less favorable *IL28B* genotype efficacy issues prevail. The effect of extending pegIFN/RBV treatment duration or adding a third or fourth agent on SVR rates needs to be studied. These possible strategies should be assessed prospectively in randomized controlled trials stratified to *IL28B* type.

Clinical message: Host IL28B genotype may allow for shortened treatment regimens in favorable C/C genotype patients, particularly with regimens including DAAVs.

Review of existing trial data is now required where possible to determine whether knowledge of host genotype alters the interpretation of a study. Stratification for host *IL28B* genotype to avoid imbalance in treatment arms is of particular concern for early phase trials with small sample sizes. Ongoing trials involving IFN-λ, other developing immunomodulator therapies and directly acting antivirals are awaited with interest.

Clinical message: The genetic signal of this discovery is strong and consistent and establishes the biological principle for further clinical research. More data are now required to fully explore and understand the implications in different clinical scenarios.

CONCLUSION

GWAS have identified a strong association between host *IL28B* genotype and response to treatment with pegIFN/RBV for patients with genotype 1 chronic hepatitis C. Its differential racial distribution explains much of observed clinical differences in response between races. Although this discovery has great biological plausibility, the causal variant is yet to be identified. The nature of the interaction between type I and type III IFN signaling needs to be further elucidated and should be a focus for research.

The decision to treat remains complex. Genotyping of this polymorphism will aid clinical decision making for both current standard of care and potentially for the integration of other agents in the future, providing an opportunity for clinicians to individualize treatment regimens for hepatitis C patients.

CONFLICT OF INTEREST

Guarantor of the article: Paul J. Clark, MD.

Specific author contributions: None.

Financial support: P.J.C. and A.J.T. received funding support from the Duke Clinical Research Institute, the Richard B. Boebel Family Fund, and the Gastroenterology Society of Australia. A.J.T. received funding from the National Health and Medical Research Council of Australia and the Royal Australasian College of Physicians. The IDEAL study was funded by Schering-Plough Research Institute, Kenilworth, New Jersey.

Potential competing interests: McHutchison has received research and grant support from Schering-Plough. McHutchison has received consulting fees and acted in an advisory capacity for Schering-Plough. McHutchison and Thompson are co-inventors of a patent application based on the *IL28B* finding.

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