Genome Medicine

RESEARCH HIGHLIGHT

Interleukin-28B polymorphisms and hepatitis C virus clearance

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Abstract

In 2009, several independent studies revealed a strong association between genetic variation in the interleukin-28B (*IL28B*) locus and the outcome of treatment for chronic infection with hepatitis C virus (HCV). Hundreds of studies followed, and a recent meta-analysis reports more precise odds ratios than previously published for associations between commonly reported *IL28B* polymorphisms and spontaneous HCV clearance or treatment outcome. These results should facilitate the interpretation of *IL28B* genotyping as part of personalized treatment approaches.

IL28B polymorphisms and hepatitis C virus infection

The recent literature on chronic hepatitis C virus (HCV) infection suggests that genetic variants in the human interleukin-28B (*IL28B*) locus, on chromosome 19, have an important role in response to therapy. The seven major viral genotypes have different geographical distributions and susceptibilities to interferon-α treatment. HCV genotype 1 is the most common genotype worldwide and one of the most difficult to treat [1]. Even with pegylated interferon-α and ribavirin combination therapy, the current standard treatment for HCV infection, only about half of all patients infected with HCV genotype 1 clear the virus. This poor response to therapy prompted a search for genetic and environmental factors that influence the response to therapy. Differences among ethnic groups in response to treatment of HCV infection have long suggested a genetic contribution to treatment response [2], but candidate gene studies focusing on genes involved in the response to HCV infection revealed single nucleotide polymorphisms (SNPs) with only relatively modest effects.

In 2009, however, a series of independent genome-wide association studies using high-throughput methods to screen representative SNPs throughout the genome were published [3-5]. These studies showed that patients who were infected with HCV genotype 1 were significantly more likely to achieve a sustained virological response with pegylated interferon-α plus ribavirin combination therapy if they had a common variant in the *IL28B* locus (rs12979860 C/C or rs8099917 T/T). Another study showed that patients with the rs12979860 C/C genotype were also more likely to spontaneously clear the virus even without treatment [6]. These reports have since inspired hundreds of studies examining the role of *IL28B* in HCV infection in other ethnic groups and with other HCV genotypes. However, there is little consensus about which SNP (rs12979860, rs8099917, or another SNP) is most strongly associated with response to therapy, and the size of the effect varies widely among studies. None of the commonly reported SNPs is, therefore, likely to be the functional SNP, and the identity of the functional SNP and the underlying mechanism have not yet been reported. In addition, the functional variant may be difficult to identify using conventional genotyping methods (for example, by searching for insertion/deletion or structural variants). However, thousands of individuals have already been genotyped for rs12979860 and/or rs8099917, and both SNPs seem to be strongly linked to the underlying functional SNP. Carrying out a meta-analysis of existing studies is, therefore, one way to gain additional insight into the role of these SNPs in HCV infection.

Lessons on HCV clearance from a meta-analysis

Maria Jiménez-Sousa *et al.* [7] have now performed a rigorous meta-analysis of the *IL28B* polymorphism literature to characterize the size of the effect of each commonly reported SNP, collectively and with the studied populations stratified into subgroups. Although several *IL28B*

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meta-analyses have been reported previously, these were limited by the number of available studies, as well as the number of SNPs and subgroups examined. Many relevant studies were published in 2011 and 2012 and were, therefore, not included in earlier meta-analyses (reviewed in [1]). The large number of available studies has allowed Jiménez-Sousa *et al*. to apply stricter study inclusion criteria without sacrificing statistical power. Their meta-analysis is also the first to explicitly examine the role of *IL28B* polymorphisms in spontaneous clearance of HCV.

The goal of meta-analysis is to aggregate data from multiple independent studies to improve statistical power, with the aim of detecting smaller effects and increasing the accuracy of estimates of model parameters and of the size of the effect. The success of this approach is also partly due to the use of standardized guidelines that recommend excluding studies that violate predetermined criteria, thereby reducing noise and ensuring that the included studies are more homogeneous and easily comparable [8]. Jiménez-Sousa *et al*. identified 282 publications through a PubMed search involving keywords associated with *IL28B* and HCV therapy. Two researchers independently evaluated each study for homogeneity on the basis of several criteria. Studies involving co-infection with hepatitis B virus or a treatment duration of less than 24 weeks, for example, were excluded. Data were extracted using a consensus approach, and the original authors were consulted where necessary. Meta-analysis assumes that each study is independent; however, in practice, several studies may examine different aspects of the same cohort. In such cases, Jiménez-Sousa *et al*. selected only one study for inclusion. Sensitivity analysis was also used to identify studies that excessively influenced the pooled results. Because the effect of *IL28B* polymorphisms varies among ethnic groups and HCV genotypes, the data from studies involving heterogeneous groups were divided into subgroups and compared separately. Rigorous definitions of sustained virological response and spontaneous clearance were used to ensure the comparability of endpoints among the studies. Each study was also assigned a quality score of +1, 0, or -1 using a standard scoring system.

Ultimately, only 74 of the 282 published studies met all of the criteria and were included in the meta-analysis. Of the 21 significant *IL28B* SNPs reported in the literature, only eight were able to be included in the meta-analysis. Of these, rs12979860 and rs8099917 were by far the most commonly reported, and each had been assessed in about 12,000 patients for association with sustained virological response and in approximately 2,000 patients for association with spontaneous clearance. Most patients were either Caucasian or Asian, and half of the studies included only patients infected with HCV genotype 1. Heterogeneous groups were analyzed separately according to ethnicity, HCV genotype, and the presence of HIV co-infection.

The SNP that was most strongly associated with sustained virological response was rs12979860, with an effect size of odds ratio (OR) = 3.77, based on meta-analysis of 42 studies. The effect size varied with ethnicity, being smallest among North Africans (OR = 1.67) and largest among Hispanics (OR = 7.17), although the effect sizes at these extremes were based on a small number of studies. The effect size for the hard-to-treat genotypes, genotypes 1 and 4 (OR = 4.20), was significantly larger than for genotypes 2 and 3 (OR = 1.59).

For rs8099917, meta-analysis of 39 studies indicated an overall effect size of OR = 3.86 for sustained virological response. This effect size was larger than that of rs12979860 (OR = 3.77), but heterogeneity analysis highlighted six studies that included mainly Japanese individuals. When these studies were excluded, the overall effect size for rs8099917 was OR = 3.27, which suggests that this SNP may be more strongly associated with sustained virological response in Asians (OR = 4.82) than in Caucasians (OR = 2.71). As was the case for rs12979860, the size of the effect was stronger for genotypes 1 and 4 (OR = 4.55) than for genotypes 2 and 3 (OR = 1.59).

Although relatively few studies were available for meta-analysis of spontaneous clearance, both SNPs had comparable effect sizes (rs12979860, OR = 3.20; and rs8099917, OR = 3.60). However, subgroup analysis for rs12979860 showed that ethnicity influenced effect size, with a larger effect size among Caucasians (OR = 3.78) than Asians (OR = 1.31). The effect size was also larger for HCV genotype 1 (OR = 5.66) than for all genotypes assessed together (OR = 2.34).

Perspectives

Although the meta-analysis by Jiménez-Sousa *et al*. reveals few surprises, the study provides refined estimates of the probability of a sustained virological response and spontaneous clearance in individuals with a favorable *IL28B* genotype, and it compares the effect sizes of associations among ethnic groups and HCV genotypes. Importantly, this meta-analysis also provides a useful evaluation of many of the major studies involving *IL28B* polymorphisms. Although Jiménez-Sousa *et al*. detected several articles that reported conflicting results or excessively influential results, overall their meta-analysis found remarkable consistency among the studies on *IL28B* SNPs and treatment of chronic HCV infection.

Some researchers, however, have argued that *IL28B* SNP testing arrived ten years too late [9]. In 2011, the US Food and Drug Administration approved the use of telaprevir, the first in a class of new direct-acting antiviral drugs, for the treatment of chronic infection with HCV genotype 1. Based on the results of several large phase 2

and 3 clinical trials (for example, PROVE, ADVANCE, ILLUMINATE, and REALIZE), the addition of telaprevir to the standard combination therapy is expected to lead to higher sustained virological response rates, including in patients who have relapsed or who failed to respond to pegylated interferon-α and ribavirin combination therapy (reviewed in [9]). Ultimately, it is hoped that a combination therapy involving two or more direct-acting antiviral drugs will replace interferon-α-based therapy, in which case the interest in *IL28B* polymorphisms is likely to wane. However, not all patients are eligible for telaprevir therapy, and therapy for chronic HCV infections is likely to continue to require interferon-α and ribavirin to suppress viral breakthrough until robust interferon-α-free therapies are developed. *IL28B* polymorphisms might also influence the response to triple therapy [10], but additional studies are needed before this can be addressed through meta-analysis.

The switch to triple therapy also means that fewer new studies based on the current standard combination therapy are likely to be published. Therefore, the study by Jiménez-Sousa *et al*. arrives at an important crossroads in the treatment of HCV infection. Knowledge of patients' *IL28B* genotypes might help to identify those who are likely to benefit from therapy of a shorter duration than usual or to respond to conventional therapy alone and could, therefore, be spared exposure to telaprevir [9]. The often overlooked role of *IL28B* polymorphisms in spontaneous clearance may also receive more attention. Although the most effective use of *IL28B* genotype data in clinical practice remains unclear, the comprehensive and up-to-date estimates in the meta-analysis by Jiménez-Sousa *et al*. will help to facilitate the development of a more personalized approach to HCV therapy.

Abbreviations

HCV, hepatitis C virus; *IL28B*, interleukin-28B gene; OR, odds ratio; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

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References

1. Hayes CN, Imamura M, Aikata H, Chayama K: **Genetics of *IL28B* and HCV-response to infection and treatment.** *Nat Rev Gastroenterol Hepatol* 2012, **9:**406-417.
2. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, Nelson KE, Strathdee SA, Johnson L, Laeyendecker O, Boitnott J, Wilson LE, Vlahov D: **The natural history of hepatitis C virus infection: host, viral, and environmental factors.** *JAMA* 2000, **284:**450-456.
3. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB: **Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance.** *Nature* 2009, **461:**399-401.
4. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J: ***IL28B* is associated with response to chronic hepatitis C interferon-α and ribavirin therapy.** *Nat Genet* 2009, **41:**1100-1104.
5. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M: **Genome-wide association of *IL28B* with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C.** *Nat Genet* 2009, **41:**1105-1109.
6. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M: **Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus.** *Nature* 2009, **461:**798-801.
7. Jiménez-Sousa M, Fernández-Rodríguez A, Guzmán-Fulgencio M, García-Álvarez M, Resino S: **Meta-analysis: implications of interleukin-28B polymorphisms in spontaneous and treatment-related clearance for patients with hepatitis C.** *BMC Med* 2013, **11:**6.
8. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *J Clin Epidemiol* 2009, **62:**1006-1012.
9. Jensen DM, Pol S: ***IL28B* genetic polymorphism testing in the era of direct acting antivirals therapy for chronic hepatitis C: ten years too late?** *Liver Int* 2012, **Suppl 1:**74-78.
10. Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Chayama K, Nakamura Y, Kumada H: **Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin.** *Hepatology* 2010, **52:**421-429.

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