Published in final edited form as:
*Hepatology*. 2014 April ; 59(4): 1650–1651. doi:10.1002/hep.26675.

# Disease progression during advanced fibrosis: *IL28B* genotype or HCV RNA levels?

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**Keywords**

IFNL3; acute; chronic; HCV RNA

## To the editor

We read with interest the paper from Noureddin et al. demonstrating that *interleukin-28B (IL28B)* CC genotype was associated with greater hepatic inflammation, higher ALT and worse clinical outcomes in patients with chronic hepatitis C virus (HCV) infection (1). However, we wonder whether the authors considered adjusting for HCV RNA levels? The hypothesis would be that the relationship between *IL28B* CC genotype and increased disease progression may be confounded by HCV RNA levels in those with the *IL28B* CC genotype.

Individuals with the *IL28B* CC genotype have higher HCV RNA levels during acute (2) and chronic (3) infection. In the InC$^3$ Study, a collaborative of nine prospective international cohorts of acute HCV infection (4), among those with untreated persistent HCV infection and HCV RNA levels 12 months following infection (n=224), male gender (vs. female, AOR=2.38;95% CI=1.19–4.76;*P*=0.02), *IL28B* CC genotype (vs. TT/CT, AOR=2.26;95% CI=1.21–4.20;*P*=0.03), and HCV genotype 1 (vs. genotype 3, AOR=2.13;95% CI=1.03–4.55;*P*=0.04) were independently associated with high HCV RNA levels at 12 months following infection.

Although studies have suggested that HCV RNA levels are not associated with disease progression (5), HCV RNA may mediate liver disease progression by cumulative HCV RNA exposure (over the duration of infection) or by absolute HCV RNA levels (via immune responses and/or hepatic inflammation). It is possible that HCV RNA levels have greater clinical effect in later stages of liver disease.

To better understand the independent effect of *IL28B* genotype on HCV natural history, the impact of HCV RNA levels should be considered as a potential confounder which may partially explain or contribute to the observed associations or lack thereof. This important

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**Disclosures:** JG is a consultant/advisor for Merck. GD is a consultant/advisor and has received research grants from Roche, Merck, Janssen, Gilead, Bristol Myers Squibb.

work could shed light on whether increased HCV RNA levels or cumulative HCV RNA exposure among those with *IL28B* CC genotype has any impact on HCV natural history during advanced disease. We urge the authors to assess whether HCV RNA levels and duration infection were associated with outcomes measured in their study and whether this varied by *IL28B* genotype.

## Acknowledgments

**Financial Support:** The InC$^3$ Study is supported by the National Institute on Drug Abuse Award Number R01DA031056. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. The Kirby Institute is funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. JGr is supported by a National Health and Medical Research Council (NHMRC) Career Development Fellowship. GD is supported by an NHMRC Practitioner Research Fellowship.

## List of Abbreviations

| | |
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| **IL28B** | interleukin-28B |
| **HCV** | Hepatitis C virus |
| **PWID** | people who inject drugs |

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