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The genetics of spontaneous clearance of hepatitis C virus infection: A complex topic with much to learn

Jason Grebely¹, Gregory J. Dore¹, Arthur Y. Kim², Andrew Lloyd³, Naglaa H. Shoukry⁴, Maria Prins⁵, and Kimberly Page⁶

¹The Kirby Institute, UNSW Australia, Sydney, Australia ²Harvard Medical School, Boston, MA, USA ³Inflammation and Infection Research Centre, School of Medical Sciences, UNSW Australia, Sydney, Australia ⁴CRCHUM, Université de Montréal, Montreal, QC, Canada ⁵GGD Public Health Service of Amsterdam, Amsterdam, The Netherlands ⁶Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

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To the editor

We appreciate the insightful comments by Alric et al. highlighting the role of the DQB1*0301 allele of the major histocompatibility complex class II (HLA class II) and spontaneous HCV clearance (1, 2). The demonstration that the DQB1*0301 allele is associated with spontaneous HCV clearance, independent of *interferon-λ3* genotype (*IFNL3*) genotype, is an important advance in our understanding of host factors important in control of HCV infection (2).

Up until recently, the International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC³) Study has relied on the availability of data that has already been collected from the contributing cohorts (3, 4). Many of the cohorts have not performed HLA-DQ or DR locus genotyping, so this could not be included in this analysis. However, the Laboratory Steering Committee of the InC³ study (chaired by Andrew Lloyd from UNSW Australia and Naglaa Shoukry from the Université de Montréal), has initiated a protocol for the collection of DNA samples from each cohort which will be available for future genetic research (led by Arthur Kim from Harvard Medical School). As such, it will be possible to assess the association of the DQB1*0301 allele with spontaneous HCV clearance within our cohort in the near future.

Corresponding Author: Jason Grebely, PhD, Senior Lecturer, Viral Hepatitis Clinical Research Program, The Kirby Institute, UNSW Australia, Phone: +61-2-9385 0957 Fax: +61-2-9385 0876, jgrebely@kirby.unsw.edu.au.

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Interestingly, in the large genome wide association study, only 15% of the variance of spontaneous clearance was attributed to the two SNPs related to DQB1*0301 (2), suggesting that other host, environmental and viral factors are likely involved in spontaneous HCV clearance. This also highlights the complexity of trying to understand factors important in the control of HCV infection. Host polymorphisms related to genes encoding proteins associated with innate or adaptive immunity such as HLA class I and II, tapasin, natural-killer-cell receptors, chemokine receptors, interleukins, toll like receptors and interferon-stimulated genes have been associated with control of HCV (5–7). However, often the identified genetic associations have not been confirmed in independent cohorts, differ in diverse populations, and studies are limited by small sample size or varying definitions of HCV outcome; moreover, little is known about their functional basis (5–7). The large genome wide association study performed by Duggal and colleagues has helped advance our knowledge in this area and highlights the importance of the genetic role of HLA Class II and *IFNL3* genotype in spontaneous HCV clearance (2). Additional research is needed to ascertain the mechanisms through which these genes and others affect the outcome of HCV infection.

While the hypothesis posed by the authors that the association of DQB1*0301 and *IFNL3* genotype may abolish the observed effect of female sex is interesting, there are no data yet to support this hypothesis and answering this question should be a focus of future studies. In the study by Duggal et al, the HLA class II association was detected in both men and women (2).

The availability from the well-defined cases of acute HCV with spontaneous HCV clearance from the InC³ Study will form a valuable tool for future research to assess novel genetic markers associated with spontaneous HCV clearance. It is hoped that this information will assist with HCV vaccine design and lead to better global control of HCV infection.

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List of Abbreviations

<i>IFNL3</i>	<i>interferon-λ3</i>
HCV	Hepatitis C virus
PWID	people who inject drugs

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