Impact of Host Genetic Variants on Natural History and Treatment of Hepatitis C Virus Infection

Akademisk avhandling

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The thesis is based on the following papers:

I. Rembeck K, Maglio C, Lagging M, Christensen PB, Färkkilä M, Langeland N, Buhl MR, Pedersen C, Mørch K, Norkrans G, Hellstrand K, Lindh M, Pirazzi C, Burza MA, Romeo S, Westin J. *PNPLA 3* I148M genetic variant associates with insulin resistance and baseline viral load in HCV genotype 2 but not in genotype 3 infection. *BMC Medical Genetics 2012, 13:82*

II. Rembeck K, Alsiö Å, Christensen PB, Färkkilä M, Langeland N, Buhl MR, Pedersen C, Mørch K, Westin J, Lindh M, Hellstrand K, Norkrans G, Lagging M. Impact of *IL28B*-Related Single Nucleotide Polymorphisms on Liver Histopathology in Chronic Hepatitis C Genotype 2 and 3. PLoS One. 2012;7(1):e29370.

III. Rembeck K, Westin J, Lindh M, Hellstrand K, Norkrans G, Lagging M. Association Between Interleukin-28B-Related Genetic Variants and Liver Histopathology Differs Between Hepatitis C Virus Genotypes. *Hepatology. 2012; 56(1):394.*

IV. Ydreborg M, Westin J, Rembeck K, Lindh M, Norrgren H, Holmberg A, Wejstål R, Norkrans G, Cardell K, Weiland O, Lagging M. Impact of *IL28B*-Related Single Nucleotide Polymorphisms on Liver Transient Elastography in Chronic Hepatitis C Infection. *PLoS One. 2013; 8(11):e80172*

V. Rembeck K, Waldenström J, Hellstrand K, Nilsson S, Nyström K, Martner A, Lindh M, Norkrans G, Westin J, Pedersen C, Färkkilä M, Langeland N, Buhl MR, Mørch K, Christensen PB, Lagging M. Variants of the Inosine Triphosphate Pyrophosphatase Gene Are Associated with Reduced Relapse Risk Following Treatment for HCV Genotype 2/3. *Hepatology. 2014; 59(6):2131-9*

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ABSTRACT

Chronic hepatitis C Virus (HCV) infection causes liver disease and may progress to severe fibrosis, cirrhosis, and hepatocellular carcinoma. This thesis aimed to evaluate the impact of host genetics, i.e. genetic variants of *PNPLA3*, *IL28B* and *ITPA*, on liver disease severity and treatment outcome in HCV genotype 2 and 3 infected patients treated with pegylated interferon and ribavirin for either 12 or 24 weeks.

In paper I, 359 patients were evaluated retrospectively with regards to the impact of the *PNPLA3* genetic variants. No significant impact was observed on liver disease severity nor on treatment outcome, and the clinical need to screen Nordic HCV genotype 2 or 3 infected patients for these genetic variants seems low.

In papers II and III, in post-hoc evaluation encompassing 339 Nordic HCV genotype 2 or 3 infected patients, genetic variants of the *rs12979860* in proximity to *IL28B* were not associated with treatment outcome but the $CC_{rs12979860}$ and the $TT_{rs8099917}$ genetic variants (n=314) were found to be associated with more pronounced liver histopathology among HCV genotype 3 infected patients. Thus, these patients may benefit from early initiation of therapy.

In paper IV, in a real life trial (n=737) enrolling HCV genotype 1-3 infected patients evaluated by means of transient elastography, $CC_{rs12979860}$ was significantly associated with higher liver stiffness values among HCV genotype 3 infected patients; thus confirming the results of papers II and III in an independent cohort of patients.

In paper V, in a post-hoc analysis of Nordic HCV genotype 2 or 3 infected patients treated with 800 mg ribavirin daily and interferon, reduced ITPase (n=354) activity was significantly associated with increased likelihood of achieving sustained virological response. Thus the majority of patients having normal ITPase activity may benefit more from a higher weight-based dosing of ribavirin.

Keywords: Hepatitis C virus, host genetics, PNPLA3, IL28B, ITPA

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