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IFN STIMULATED GENE EXPRESSION IN THE LIVER IS A BETTER PREDICTOR OF TREATMENT RESPONSE IN CHRONIC HEPATITIS C THAN THE *IL28B (IFNλ3)* GENOTYPE

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Background: Therapy of chronic hepatitis C (CHC) with pegIFNa/ribavirin achieves sustained virologic response (SVR) in ~55%. Pre-activation of the endogenous interferon system in the liver is associated non-response (NR). Recently, genome-wide association studies described associations of allelic variants near the *IL28B (IFNλ3)* gene with treatment response and with spontaneous clearance of the virus. We investigated if the *IL28B* genotype determines the constitutive expression of IFN stimulated genes (ISGs) in the liver of patients with CHC.
Methods: We genotyped 93 patients with CHC for 3 *IL28B* single nucleotide polymorphisms (SNPs, rs12979860, rs8099917, rs12980275), extracted RNA from their liver biopsies and quantified the expression of *IL28B* and of 8 previously identified classifier genes which discriminate between SVR and NR (*IFI44L, RSAD2, ISG15, IFI22, LAMP3, OAS3, LGALS3BP* and *HTATIP2*). Decision tree ensembles in the form of a random forest classifier were used to calculate the relative predictive power of these different variables in a multivariate analysis.
Results: The minor *IL28B* allele (bad risk for treatment response) was significantly associated with increased expression of ISGs, and, unexpectedly, with decreased expression of *IL28B*. Stratification of the patients into SVR and NR revealed that ISG expression was conditionally independent from the *IL28B* genotype, i.e. there was an increased expression of ISGs in NR compared to SVR irrespective of the *IL28B* genotype. The random forest feature score (RFFS) identified *IFI27* (RFFS = 2.93), *RSAD2* (1.88) and *HTATIP2* (1.50) expression and the HCV genotype (1.62) as the strongest predictors of treatment response. ROC curves of the *IL28B* SNPs showed an AUC of 0.66 with an error rate (ERR) of 0.38. A classifier with the 3 best classifying genes showed an excellent test performance with an AUC of 0.94 and ERR of 0.15. The addition of *IL28B* genotype information did not improve the predictive power of the 3-gene classifier.
Conclusions: *IL28B* genotype and hepatic ISG expression are conditionally independent predictors of treatment response in CHC. There is no direct link between altered IFNλ3 expression and pre-activation of the endogenous system in the liver. Hepatic ISG expression is by far the better predictor for treatment response than *IL28B* genotype.

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