Genome-wide association study identifies variants associated with progression of liver fibrosis from HCV infection


BACKGROUND & AIMS
Polymorphisms in IL28B were shown to affect clearance of hepatitis C virus (HCV) infection in genome-wide association (GWA) studies. Only a fraction of patients with chronic HCV infection develop liver fibrosis, a process that might also be affected by genetic factors. We performed a 2-stage GWA study of liver fibrosis progression related to HCV infection.

METHODS
We studied well-characterized HCV-infected patients of European descent who underwent liver biopsies before treatment. We defined various liver fibrosis phenotypes on the basis of METAVIR scores, with and without taking the duration of HCV infection into account. Our GWA analyses were conducted on a filtered primary cohort of 1161 patients using 780,650 single nucleotide polymorphisms (SNPs). We genotyped 96 SNPs with P values <5 × 10(-5) from an independent replication cohort of 962 patients. We then assessed the most interesting replicated SNPs using DNA samples collected from 219 patients who participated in separate GWA studies of HCV clearance.

RESULTS
In the combined cohort of 2342 HCV-infected patients, the SNPs rs16851720 (in the total sample) and rs4374383 (in patients who received blood transfusions) were associated with fibrosis progression (P(combined) = 8.9 × 10(-9) and 1.1 × 10(-9), respectively). The SNP rs16851720 is located within RNF7, which encodes an antioxidant that protects against apoptosis. The SNP rs4374383, together with another replicated SNP, rs9380516 (P(combined) = 5.4 × 10(-7)), were linked to the functionally related genes MERTK and TULP1,
which encode factors involved in phagocytosis of apoptotic cells by macrophages.

CONCLUSIONS
Our GWA study identified several susceptibility loci for HCV-induced liver fibrosis; these were linked to genes that regulate apoptosis. Apoptotic control might therefore be involved in liver fibrosis.