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Using genomics and metabolism to discover novel genes regulating development of liver fibrosis

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Abstract

The histological and biochemical progression of liver disease is similar in alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH), we hypothesized that the genetic susceptibility to these liver diseases would be similar. To identify potential candidate genes that regulate the development of liver fibrosis, we studied a chromosome substitution strain (CSS-17) that contains chromosome 17 from the A/J inbred strain substituted for the corresponding chromosome on the C57BL/6J (B6) genetic background. Previously we identified quantitative trait loci (QTLs) in CSS-17, namely obesity resistant QTL13 and QTL 15 (*Obrq13 and Obrq15,* respectively*),* that were associated with protection from diet-induced obesity and hepatic steatosis on a high fat diet.To test if these or other CSS-17 QTLs conferred resistance to alcohol-induced liver injury and fibrosis, B6, A/J, CSS-17 and congenics 17C-1 and 17C-6 were either fed Lieber DeCarli ethanol-containing diet or had carbon tetrachloride (CCl_4) administered chronically.

The congenic strain carrying *Obrq15* showed resistance from alcohol-induced liver injury and liver fibrosis, whereas *Obrq13* conferred susceptibility to liver fibrosis. From published deep sequencing data for chromosome 17 in the B6 and A/J strains, we identified candidate genes in *Obrq 13* and *Obrq15* that contained single nucleotide polymorphisms (SNPs) in the promoter region or within the gene itself. NADPH oxidase organizer 1 (*Noxo1*) and NLR family, CARD domain containing 4 (*Nlrc4*) showed altered hepatic gene expression in strains with the A/J allele at the end of the ethanol diet study and after CCl_4 treatment.

Aspects of the genetics for the progression of ASH are unique compared to NASH, suggesting that the molecular mechanisms for the progression of disease are at least partially distinct. Using these CSSs we identified two candidate genes, *Noxo1* and *Nlrc4,* which modulate genetic susceptibility in ASH.