

## NOVEL GENETIC MARKERS ASSOCIATED WITH RISK OF NON-ALCOHOLIC STEATOHEPATITIS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASES

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**Background.** Obesity and insulin resistance are associated with non-alcoholic fatty liver disease (NAFLD). While the majority of people with these risk factors develop steatosis, only a small portion will progress to non-alcoholic steatohepatitis (NASH) or further to cirrhosis. This suggests other host factors may play an important role.

**Objective.** To identify genetic markers associated with NASH using a candidate gene approach.

**Methods.** 187 subjects with available DNA were categorized as follows: Normal (no steatosis, N=60), Steatosis (N=55), NASH (N=50) and NAFLD-related cirrhosis (N=22). All subjects had liver histology compatible with accepted diagnostic criteria (except for 10/22 of the cirrhosis group, having a robust clinical diagnosis). Initial genes of interest in this preliminary study were: 1) a missense SNP in the gene coding DEAD box polypeptide 5 (DDX5), previously reported by our group to be associated with an increased risk of fibrosis in patients with hepatitis C, and 2) four SNPs in the gene coding microsomal triglyceride transfer protein (MTP), a gene central to hepatic lipid export. The associations of each marker with steatosis, NASH and cirrhosis were adjusted for ethnicity (white and non-white), and risk factors, including body mass index (BMI), age, gender, type II diabetes, and AST/ALT ratio.

**Results.** In the Normal group (control), 88% had a BMI > 30, and 13.3% were diabetic compared to 82% and 26% in the NASH group (case) respectively. The DDX5 SNP was associated with an increased risk of NASH compared with both the Steatosis group (OR=22.3, p=0.005) and the Normal group (OR=3.7, p=0.04). Of the four MTP SNPs genotyped, associations were observed for two: I128T and N166S. 128T was associated with a decreased risk of NASH relative to both the Steatosis group (OR=0.4, p=0.05) and the Normal group (OR=0.2, p=0.0001). 166S was associated with an increased risk of NASH when compared to the Normal group (OR=17.4, p=0.004). None of the SNPs was associated with risk of cirrhosis relative to the NASH group.

**Conclusions.** Our preliminary study suggests DDX5 and MTP variants are associated with risk of developing NASH in patients with NAFLD in a unique study population containing matched, histologically normal controls. The potential involvement of these SNPs in the development and progression of NAFLD will require confirmation in larger study groups and determination of their precise functional significance.