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Non-alcoholic Fatty Liver Disease (NAFLD)

Mentor:
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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in Western countries in which men and women are affected equally (de Alwis and Day 2008; Willner et al. 2001). The prevalence and severity of NAFLD increase with obesity (Flegal et al. 1998 & 2003). Since obesity is known to have a genetic etiology, we propose that genetic factors influence susceptibility to non-alcoholic fatty liver disease. To evaluate this hypothesis, we select 36 genes related to metabolic syndrome, or to NAFLD pathogenesis in the domains of adiposity, pattern of fat deposition, insulin sensitivity, lipid storage and export, hepatic fatty acid oxidation, the magnitude of oxidative stress, and hepatic fibrosis to test for association with NAFLD. We focus on 4 primary phenotypes in 974 Caucasian subjects, many of whom underwent two clinical visits approximately 8 years apart, from the NHLBI Family Heart Study (FHS) (Higgins et al. 1996): ALT, Liver Attenuation (LA), LA adjusted for Body Mass Index (LA_BMI), and NAFLD status. The first three phenotypes are quantitative while the last phenotype is qualitative. NAFLD status is an indicator of NAFLD which captures not only individuals with fatty liver, but those also having evidence of liver damage as measured by ALT. Subjects positive for hepatitis C antibodies, heavy alcohol consumption (>20 drinks/week), and medication use for high blood pressure, diabetes, or cholesterol that resulted in elevated levels of ALT are excluded from analysis. We extracted 375 genotyped SNPs within all exons and introns, as well as 2kb upstream and 1kb downstream of each gene to examine putative transcription factor binding sites and 3’ UTR regulatory regions. Each phenotype is entered into the linear mixed model with the sandwich option in which one SNP is tested at a time for all 375 SNPs. Based on gene-wise critical value derived from SimpleM (Gao et al. 2008), four genes reached significance in association with at least one phenotype in our analysis; these 4 genes include PNPLA3, SAMM50, SOD2, and CHUK. We further examined these signal regions by testing imputed SNPs within the defined gene boundaries. Manhattan plots were generated for each significant phenotype by gene combination to better localize the signal.