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LIPID METABOLISM GENE POLYMORPHISMS AND RISK OF FATTY LIVER IN ADOLESCENTS: A POPULATION BASED COHORT STUDY

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Nonalcoholic fatty liver disease (NAFLD) is a heritable disease resulting from altered hepatic triglyceride metabolism. We examined the association between polymorphisms in genes involved in hepatic triglyceride hydrolysis and transport and fatty liver in a population based cohort of adolescents. Methods: Adolescents (n=1,170) from the population-based Western Australian Pregnancy (Raine) Birth Cohort underwent detailed phenotypic characterisation at age 17 including hepatic ultrasound, detailed questionnaires, anthropometry and biochemical testing. DNA was extracted and 32 SNPs in lipid metabolism genes (ApoB100, ATGL, ABHD5, MTTP, CETP) with a minor allele frequency >0.1 were genotyped. Multivariate modelling was used to investigate associations between SNPs and fatty liver. Final analyses focused on 773 Caucasian adolescents with complete phenotype and genotype data. Multiple testing was accounted for using a false discovery rate of 10%. Results: Fatty liver was diagnosed by ultrasound in 133/773 (17.2%) of the Raine participants (12.7% male vs. 21.8% female, p=0.001). Adolescents with fatty liver had higher measures of adiposity (skin fold-thickness, BMI, waist circumference) and insulin resistance (HOMA-IR) than adolescents without fatty liver (all P<0.001). No significant associations were identified between ALT or serum triglyceride and the 32 SNPS. In both sexes, the minor allele of rs3774792 (abhydrolase domain containing 5 (ABHD5) gene) was associated with an increased risk of fatty liver (OR=2.54, 95%CI 1.41-4.58, p=0.002). In females, but not males, the minor alleles in two SNPS in cholesterol ester transport protein (CETP) gene were associated with reduced risk of fatty liver: rs12447924 (OR 0.21, 95% CI 0.07-0.59, p=0.003) and rs12597002 (OR=0.24, 95%CI 0.10-0.56, p=0.001). These two SNPs are in linkage disequilibrium (r2=0.6, D'=0.94). These associations were independent of BMI, skin fold thickness, HOMA-IR, HDL, triglyceride, ALT, alcohol intake, gestational age, birth weight and measures of nutrition. There was no interaction between SNP's and measures of adiposity. The associations between SNPs in ABHD5, CETP and fatty liver were independent with the presence of four adverse alleles increasing the risk of fatty liver nearly 8-fold (OR 7.77, 95%CI 2.67-22.63, p<0.001). Conclusions: Polymorphisms in lipid metabolism genes are associated with fatty

liver in adolescence, independent of metabolic factors, nutrition, alcohol and measures of growth. Whilst these results require replication in other populations, they may offer possibilities for early prediction of fatty liver and targeted interventions.

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