An adult-based genetic risk score for hepatic fat associates with liver and lipid traits in Danish children and adolescents

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Background and aims: Several genetic variants that associate with hepatic fat content in adults have been identified in genome-wide association studies. Their effects in children and adolescents remain unclear. The aims of this study were to test the effect of genetic variants known to associate with hepatic fat in adults, individually and combined as a genetic risk score (GRS), with cardiometabolic traits, and to investigate the predictive ability of the GRS for hepatic steatosis in children and adolescents.

Method: Children and adolescents with overweight/obesity from an obesity clinic cohort (n = 1, 843, median age 11.6 years, BMI SDS 0.26, 40.1% male) were included. Anthropometrics and biochemical parameters were measured in both cohorts. Liver fat content was measured by magnetic resonance spectroscopy in 539 individuals. We calculated a weighted GRS based on eight genetic variants known to associate with hepatic fat content in adults. Associations of individual genetic variants and the GRS with cardiometabolic traits were tested using multiple linear and logistic regression models. Receiver operating characteristic (ROC) curve analysis was performed on models based on risk factors for hepatic steatosis, and area under the curve (AUC) was calculated to evaluate model performance.

Results: Variants in PNPLA3, TM6SF2, GPAM, and GCKR were significantly associated with higher liver fat content (p < 0.01) and with distinct patterns of circulating lipids. The GRS was associated with higher liver fat content and alanine transaminase (ALT) activity in the obesity clinic cohort (p = 1.4 × 10^-10, p = 1.1 × 10^-9, respectively) and was not associated with adiposity or other metabolic traits in the population-based cohort. The GRS was associated with higher prevalence of hepatic steatosis (odds ratio [OR] per 1-unit GRS-increase: 2.18, p = 1.8 × 10^-13), and with lower prevalence of dyslipidemia (OR 0.90, p = 0.02). A prediction model for hepatic steatosis including GRS alone yielded cross-validated AUC of 0.76 (95% CI 0.69–0.83). The addition of the GRS to a model containing clinical risk factors for hepatic steatosis (BMI SDS, ALT, homeostatic model assessment of insulin resistance [HOMA-IR]) increased AUC slightly from 0.87 (95% CI 0.82–0.92) to 0.89 (95% CI 0.84–0.94).

Conclusion: The adult-based GRS for hepatic fat was associated with liver fat content, liver enzymes, and lipid profiles, but was not associated with adiposity and other metabolic traits in children and adolescents. The GRS could serve as a predictor of the risk for hepatic steatosis in addition to clinical risk factors and could be used for early preventative initiatives.