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

Huang, Yun; Stinson, Sara; Juel, Helene Baek; Lund, Morten; Holm, Louise Aas; Fonvig, Cilians Esmann; Grarup, Niels; Pedersen, Oluf; Christiansen, Michael Michael; Krag, Aleksander; Stender, Stefan; Holm, Jens-Christian; Hansen, Torben

Published in:
Journal of Hepatology

DOI:
10.1016/S0168-8278(22)01233-8

Publication date:
2022

Document version
Publisher's PDF, also known as Version of record

Document license:
Unspecified

Citation for published version (APA):
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 11.7 years, body mass index standard deviation score [BMI SDS] 2.85, 45.2% male) and a population-based cohort of children and adolescents (n = 2, 271, 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 hepatic steatosis, defined as hepatic fat ≥5% were calculated to evaluate model performance. 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 liver disease 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.

Background and aims: To integrate different liver gene-expression datasets to identify novel potential serological biomarkers to follow-up steatohepatitis in NALFD patients.

Method: Initial candidates were obtained by comparing the gene expression of paired liver biopsies coming from NAFLD patients that were able (n = 20) or not (n = 17) to resolve steatohepatitis at the end of a dietary or a surgical intervention of 1 year (section 1). Association of candidates to steatohepatitis was initially explored in 6 microarray gene expression datasets (n = 317) in which patients were classified as NASH or No NASH according to the SAF score and analysed as a single cohort after batch normalization. Selected candidates were filtered through a series of public datasets to retain exclusively secreted proteins able to reach the bloodstream. Candidates were validated independently in three additional RNA-seq additional datasets in which patients with Bland Steatosis (SS) were compared against patients with steatohepatitis (NASH) (Cohort 1: N = 31 SS/51 SS/16 NASH) (Cohort 2 N = 67 23 SS/44 NASH) (Cohort 3 N = 99 51 SS/47 NASH)) introducing age (Cohorts 2 and 3) and sex as covariables in the analysis (all 3). These candidates were further explored in a recently published gene expression (Govaere et al. 2020) in which 163 NASH patients were stratified by fibrosis stage (F0–F3 N = 50; F3 N = 53; F4 N = 54; F4 n = 12) and compared against patients with bland steatosis (SS) n = 51).

Results: Paired liver biopsy analysis identified 1363 genes that significantly change their behaviour specifically in patients achieving NASH resolution. 61 or them showed a positive or a negative association to steatohepatitis in the integrative multiarray comparison in the microarray multicohort dataset. 22 of them are secreted proteins able to reach the bloodstream. Only one of them, IL-32, replicated its performance in the microarray multicohort dataset (Fold Change (FC): 1.43, p-value: 9.99 × 10−5, FDR: 3.2 × 10−6). This protein also replicated its effect in the last dataset independently from fibrosis stage (NASH F0–F1 vs NAFL FC: 1.64, p-value: 3.78 × 10−6, q-value: 9.99 × 10−4 (NASH F2 vs NAFL FC: 1.69, p-value: 5.62 × 10−5, q-value: 2.90 × 10−2) (NASH F3 vs NAFL FC: 2.03, p-value: 4.81 × 10−6, q-value: 8.52 × 10−5) (NASH F4 vs NAFL FC: 2.16, p-value: 4.80 × 10−5, q-value: 1.83 × 10−4).