Combining genetics and IR-DRF, a novel measurement of insulin resistance, in predicting histological features of nonalcoholic steatohepatitis

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Summary

Background
Nonalcoholic fatty liver disease (NAFLD) is a complex disease dictated by both genetic and environmental factors. While insulin resistance (IR) is the key pathogenic driver, two common genetic variants in patatin-like phospholipase domain containing 3 (PNPLA3) and transmembrane 6 superfamily 2 (TM6SF2) also impart significant risks for disease progression. In this study, we test the hypothesis that combining genetics and a measurement of IR can predict histological features of NAFLD.

Methods
A total of 129 patients with biopsy-proven NAFLD were enrolled in this cross-sectional study with PNPLA3 I148M and TM6SF2 E167K genotypes determined by TaqMan assays. We measured the serum Insulin Resistance Diabetes Risk Factor (IR-DRF) index, a validated score that correlates with IR, using nuclear magnetic resonance. Multivariate models that included age, IR-DRF, PNPLA3, and TM6SF2 genotypes were used to study associations and predictive values for histological features of NAFLD.

Results
In this cohort, 74.4% patients had NASH with a mean NAFLD activity score (NAS) of 4.5, and 16.3% patients had advanced fibrosis (stage 3 or 4). PNPLA3 I148M variant was present in 41.1% heterozygous carriers and 21.1% homozygous carriers. About 20.9% patients carry at least one allele of the TM6SF2 E167K allele. In the multivariate analysis, IR-DRF was strongly associated with histological features of NAFLD: hepatic steatosis, lobular inflammation, NAS, and liver fibrosis (p values: <0.001 to 0.047) after adjustment for age, BMI, ALT, diabetes, and genetics. PNPLA3 and TM6SF2 genetics strongly associated with steatosis and marginally associated with inflammatory features of steatohepatitis and fibrosis (p values: 0.003 to 0.3). A multivariate model including age, diabetes, genetics, and IR-DRF strongly predicted severe hepatic steatosis (AUC 0.86) and advanced fibrosis (AUC 0.84).

Conclusions
This proof of concept study supports the hypothesis that genetics and IR are major determinants of NAFLD disease severity and demonstrates the feasibility of a new risk stratification paradigm using directly pathogenic factors.

Conclusions & Significance
NAFLD is a complex disease dictated by both genetic and environmental factors. This study supports this hypothesis by showing that age, Insulin resistance measured by IR-DRF and genetics are strongly associated with NAFLD disease severity by histology. The combination of IR-DRF and genetics shows promise as a biomarker to assist in NAFLD disease risk stratification.

Results

A multivariate model including age, diabetes, IR-DRF strongly predicts advanced fibrosis

Advanced Fibrosis (Stage 3-4)

The addition of genetics improves prediction of advanced fibrosis

Advanced Fibrosis (Stage 3-4)

The model including age, diabetes, IR-DRF, and genetics strongly predicts severe steatosis and moderately predicts NAS ≥ 5

Severe Steatosis (Score = 3) NAS (≥ 5)

Ballooning Degeneration Score NAFLD Activity Score

Fibrosis Stage

Histology

Fibrosis Stage (n)

Severe Steatosis (Score = 3) NAS (≥ 5)

Area under ROC curve = 0.8197

Area under ROC curve = 0.8360

Area under ROC curve = 0.7359

Area under ROC curve = 0.8568

Multivariate associations between IR-DRF and histologic features of NASH

Conclusions & Significance

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