Göteborg, 2023

Understanding the genetic architecture of fatty liver disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 16 Januari 2023, klockan 09:00

av Oveis Jamialahmadi

Fakultetsopponent:
Prof. Silvia Sookoian
University of Buenos Aires-CONICET, Argentina

Avhandlingen baseras på följande delarbeten

I. Bianco C*, Jamialahmadi O*, Pelusi S*, Baselli G, Dongiovanni P, Zanoni I, Santoro L, Maier S, Liguori A, Meroni M, Borroni V, D'Ambrosio R, Spagnuolo R, Alisi A, Federico A, Bugianesi E, Petta S, Miele L, Vespasiani-Gentilucci U, Anstee QM, Stickel F, Hampe J, Fischer J, Berg T, Fracanzani AL, Soardo G, Reeves H, Prati D, Romeo S, Valenti L. **Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores.** *Journal of Hepatology, 2021. doi: 10.1016/j.jhep.2020.11.024.*

II. Jamialahmadi O, Mancina RM, Ciociola E, Tavaglione F, Luukkonen PK, Baselli G, Malvestiti F, Thuillier D, Raverdy V, Männistö V, Pipitone RM, Pennisi G, Prati D, Spagnuolo R, Petta S, Pihlajamäki J, Pattou F, Yki-Järvinen H, Valenti L, Romeo S. **Exome-Wide Association Study on Alanine Aminotransferase Identifies Sequence Variants in the GPAM and APOE Associated with Fatty Liver Disease**. *Gastroenterology, 2021. doi: 10.1053/j.gastro.2020.12.023.*

III. Jamialahmadi O, Mancina RM, Ciociola E, Valenti L, Romeo S. **Gene-BMI-wide Interaction Study of Alanine Aminotransferase Identifies UXBN2A/CYP7A1 as a novel locus for Fatty Liver Disease.** *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Understanding the genetic architecture of fatty liver disease

Oveis Jamialahmadi

Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden, 2023.

Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease, ranging from simple steatosis to more severe conditions, namely non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). NAFLD has a strong genetic component, and its heritability depends on environmental factors and ethnicity. So far, genome-wide association studies were able to explain only a small fraction of its heritability, indicating the presence of missing heritability. Moreover, despite more than 20% of the general population and more than 70% of individuals with obesity have fatty liver, only a minority of individuals will progress to end stage liver disease. In the first study, we used polygenic risk scores (PRS) based on 5 known common genetic determinants of NAFLD to stratify the risk of HCC in individuals with dysmetabolism. We showed the ability of our PRS to predict the full spectrum of NAFLD and HCC both in high-risk individuals and in the general population. Additionally, we demonstrated a causal association between genetic predisposition to hepatic steatosis and HCC using a Mendelian Randomization approach. In the second study, we performed an exome-wide association study of alanine aminotransferase (ALT), a biomarker of liver fat and damage, to identify other genetic determinants of fatty liver disease. We found two missense variants on *GPAM* and *APOE* genes, robustly associated with liver fat content and chronic liver disease. Finally, in the third study, we performed a gene-environment-wide interaction study (GEWIS) of ALT to evaluate the role of gene-environment interactions in fatty liver disease susceptibility and to identify new genetic determinant of NAFLD. We found a new *locus* interacting with body mass index (BMI), the strongest environmental risk factor for NAFLD, associated with liver fat and chronic liver disease, but not with ALT.

In conclusion, these findings strongly support a causal relationship between liver fat accumulation and severe liver disease. Moreover, new genetic determinants of fatty liver identified by our analyses may be used for risk stratification of advanced liver disease and HCC, and exploited as potential drug targets.

Keywords: Non-alcoholic fatty liver disease, Polygenic risk score, Genome-wide association studies, Mendelian Randomization.

ISBN: 978-91-8069-035-5 (TRYCK) http://hdl.handle.net/2077/73763
ISBN: 978-91-8069-036-2 (PDF)