Fatty Liver Disease: Metabolic, Genetic, or Both?

Despite being the most common liver disease with a global prevalence of 25%, nonalcoholic fatty liver disease (NAFLD) is a diagnosis of exclusion and a term of negation.[1] According to the guidelines of the American Association for the Study of Liver Diseases, the diagnosis of NAFLD requires that "there is no significant alcohol consumption" as well as the absence of "competing etiologies for hepatic steatosis."[2] Considering the difficulties in reliably assessing past alcohol consumption and taking into account that hepatic steatosis is a stereotypic response to a wide range of drugs, toxins, and diseases, the diagnosis of NALFD is often based on uncertainty.[3,4] To better capture the importance of metabolic changes driving disease pathogenesis of NAFLD, the term *metabolic-associated fatty liver disease* (MAFLD) was recently adopted from a previous initiative.[5,6] Adopting this suggestion would certainly reach beyond pure semantics, because MAFLD is verifiable.[4] In clinical practice, such specific findings are a bright liver on ultrasound in patients with components of the metabolic syndrome, particularly diabetes and obesity, none of which is specific or notably sensitive. But could the diagnosis of NAFLD/MAFLD be positively affirmed by a sensitive and specific test?

Although such an unambiguous and verifiable test could theoretically be a set of genetic markers, those who are looking for such a set from a genome-wide association study (GWAS) will be disappointed. Does this mean that a GWAS in NAFLD is a lost paradigm? The answer is certainly no, because the results of a GWAS more often represent the beginning of mechanistic research into the biology of a disease than an endpoint.

In this context, the study by investigators from the Multiethnic Cohort Study at the University of Southern California led by Park et al. in the August issue of Hepatology Communications represents an important contribution to the field of NAFLD genetics.[7] In contrast to previous studies focusing on Caucasians or East Asians, the present study was conducted in a multiethnic cohort in which striking differences in hepatic triglyceride concentrations were found, ranging from a mean of 4.0% in African Americans to 6.8% in Japanese Americans. This finding suggests that hepatic steatosis is not exclusively determined by lifestyle but by genetics. Because fatty liver is defined by hepatic fat content of greater than 5%, the study population has a mild phenotype. Nevertheless, the main finding of the study is that two distinct genetic loci were found to be significantly associated with hepatic fat content as a quantitative trait. The locus on chromosome 6q13 is novel and was only associated with liver fat in Japanese Americans and native Hawaiian Americans. The other locus chromosome 22q13 is linked with the well-known p.Ile148Met variant in patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) (rs738409).

Abbreviations: GWAS, genome-wide association study; MAFLD, metabolic-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; PNPLA3, *patatin-like phospholipase domain-containing protein 3.*

Received May 1, 2020; accepted August 8, 2020.

Supported by Christian Doppler Forschungsgesellschaft (Iron and Phosphate Biology Award).

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1598

Potential conflict of interest: Nothing to report.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Heinz Zoller, M.D.
Department of Medicine and Christian Doppler Laboratory on Iron and Phosphate Biology
Medical University of Innsbruck
Anichstrasse 35
A-6020 Innsbruck, Austria
E-mail: heinz.zoller@i-med.ac.at
Tel.: +43-512-504-0

However, what about other NAFLD risk alleles previously identified in Caucasians? Variants in transmembrane 6 superfamily member 2 (*TM6SF2*) and glucokinase regulator were "weakly" associated, whereas membrane-bound O-acyltransferase domain containing 7 was only associated with liver fat in Europeans. In contrast, the recently identified protective single nucleotide variant rs6834314 in hydroxysteroid 17-beta dehydrogenase 13 was not associated with liver fat, which is not surprising. This variant was primarily identified as providing protection from progressive fibrosis and cirrhosis in NAFLD and alcoholic liver disease rather than being a genetic determinant of liver fat.[8] This negative finding highlights the importance of disentangling the different components of the complex spectrum of fatty liver phenotypes. One such component of metabolic dysfunction predominant fatty liver is insulin resistance. The risk allele in *PNPLA3* was independently associated with the homeostasis model assessment score (HOMA), a surrogate of insulin resistance. This finding confirms the link between metabolic syndrome and hepatic fat accumulation, which supports the conceptual transition from NAFLD to MAFLD. In contrast, the locus on chromosome 6q13 (rs77249491) was associated with the HOMA, but this association was lost when corrected for liver fat.

How could these findings translate into clinical practice and future research? First, the present study confirms the importance of the p.Ile148Met polymorphism in *PNPLA3* in all ethnic groups as a genetic determinant of liver fat and insulin resistance. Hence, the results further support the development of *PNPLA3*-targeted therapies for the treatment of NAFLD/MAFLD, independent of ethnicity.[9] The findings also suggest that patients with NAFLD without associated metabolic syndrome are less likely to benefit from PNPLA3-targeted therapies.

Second, the study confirms that despite the strong association between obesity and fatty liver, the two phenotypes do not share genetic risk factors. Interestingly, most genes associated with obesity are expressed in the central nervous system, whereas fatty liver genes encode proteins expressed in the peripheral organs—primarily the liver. The locus identified by Park et al.[7] that had not been previously associated with obesity or liver fat is located in an intergenic region on chromosome 6p13. With this result, the GWAS findings could represent the beginning of mechanistic research into the biology of fatty liver. What we have learned is that rs77249491 is located more than 30 kb upstream and more than 30 kb downstream from neighboring genes. Understanding how individual variants translate into disease biology can be a decade-long task, especially when variants are noncoding.

Although intronic and intergenic variants may not directly affect adjacent genes, they could have regulatory effects on more distant genetic regions. A prominent example from GWAS-based research in obesity is *FTO* (fat mass and obesity-associated alpha-ketoglutarate dependent dioxygenase). A variant in the first intron of this gene (rs9930506), whose gene product is functionally linked to protein intake, has been shown to be strongly associated with body weight and was long thought to control appetite. More recent studies demonstrate that this polymorphism more likely exerts its effect by a regulatory impact on the neighboring gene, Iroquois homeobox 3, rather than affecting *FTO* expression or function.[10] This example shows the difficulties and potential detours when it comes to the translation of genetic variants into disease mechanisms.

In conclusion, *PNPLA3* and *TM6SF2* are confirmed major genetic determinants of hepatic fat accumulation and insulin resistance in patients of different ethnic backgrounds. This genetic link advocates the positivistic diagnostic approach to patients with metabolic syndrome and a bright liver on ultrasound by simple genotyping. Eliminating the concept that this disease is more than just "NAFLD," but rather a genetically co-determined metabolic disorder, could ultimately help patients to better understand their disease and probably improve their adherence to recommended lifestyle changes.

Heinz Zoller[1,2]
Sonja Wagner[1,2]
Benedikt Schaefer[1,2]
[1]**Department of Medicine**
Medical University of Innsbruck
Innsbruck, Austria
[2]**Christian Doppler Laboratory of Iron and Phosphate Biology**
Medical University of Innsbruck
Innsbruck, Austria

REFERENCES

1) Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
2) Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.
3) Kneeman JM, Misdraji J, Corey KE. Secondary causes of nonalcoholic fatty liver disease. Therap Adv Gastroenterol 2012;5:199-207.
4) Fred HL. The diagnosis of exclusion: an ongoing uncertainty. Tex Heart Inst J 2013;40:379-381.
5) **Eslam M**, **Sanyal AJ**, George J. Toward more accurate nomenclature for fatty liver diseases. Gastroenterology 2019;157:590-593.
6) Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romer-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202-209.
7) Park SL, Li Y, Sheng X, Hom V, Xia L, Zhao K, et al. Genome-wide association study of liver fat: the Multiethnic Cohort Adiposity Phenotype Study. Hepatol Commun 2020;4: 1112-1123.
8) Abul-Husn NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. N Engl J Med 2018;378:1096-1106.
9) Dong XC. PNPLA3: a potential therapeutic target for personalized treatment of chronic liver disease. Front Med (Lausanne) 2019;6:304.
10) Speakman JR, Loos RJF, O'Rahilly S, Hirschhorn JN, Allison DB. GWAS for BMI: a treasure trove of fundamental insights into the genetic basis of obesity. Int J Obes (Lond) 2018;42: 1524-1531.

Author names in bold designate shared co-first authorship.