The dawn of a new era for nonalcoholic fatty liver disease?

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Non-alcoholic fatty liver disease (NAFLD) has become the most frequent chronic liver disease in several developed and developing countries, affecting roughly 30% of adults in the general population, 65–70% of individuals with type 2 diabetes mellitus and, virtually, all patients with obesity (1). Of note, its prevalence is believed to rise dramatically over the next decade, along with an increase of prevalence in obesity, diabetes mellitus and metabolic syndrome.

Although the disease is closely linked to insulin-resistance and obesity, the pathogenesis of NAFLD is intricate (2). Regardless of appreciable progress in our knowledge on the pathogenesis of this disease, the specific pathophysiological mechanisms implicated in the onset and progression of NAFLD remain open to question to date. Specifically, it is still debated why there are NAFLD patients that develop its advanced forms [i.e., non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma] and why there are individuals with important risk factors that have only simple steatosis. This question is very important, as several new drugs will be shortly available for the treatment of NAFLD. In this context, it is reasonable to suppose that the etiology of NAFLD is multifactorial and that genetic/epigenetic factors play an important role, together with environment, in the development and progression of NAFLD (3-5). Indeed, genetic heritability estimates of NAFLD vary widely, depending on ethnicity, study design and the methods applied for the diagnosis (6). In the last decades, many genome wide association studies have identified multiple genetic loci associated with the presence, progression and severity of NAFLD both in adults and in children and adolescents (3-5). Some of

these studies suggest a role of *PNPLA3*, *TM6SF2*, *GCKR*, *LPIN1*, *SOD2* and *KLF6* genes, that are genes implicated in the lipid handling, insulin signaling, oxidative stress and hepatic fibrogenesis (3-5). Other studies, instead, support the involvement of *MTTP*, *GPR120*, *ELOVL2*, *FADS2* and *MBOAT*7 genes, that are genes involved in the lipid metabolism and inflammation (3-5).

In a review published on *HepatoBiliary Surg Nutr* entitled "*New insights into genetic predisposition and novel therapeutic targets for nonalcoholic fatty liver disease*", Barbara and colleagues discuss in detail the genetic and epigenetic factors associated with the progression of NAFLD, the roles of proteins encoded by the common risk variants in the NAFLD pathogenesis, and the possibility of translating this information into the stratification and management of NAFLD patients, thus offering new food for thought (7).

A notion coming out from genetic studies (on NAFLD) is that specific variants in *MTTP*, *GPR120*, *ELOVL2*, *FADS2* and *MBOAT*7 may have a smaller effect size on the risk of developing NAFLD when compared to PNPLA3, TM6SF2 or GCKR variants, whose role in determining hepatic steatosis is now well established (3-5). The risk of NAFLD is closely related to the effect of these genetic variants on the hepatic fat accumulation, indicating that the deposition of lipids in hepatocytes is a relevant driver for liver injury. In particular, interestingly, combined effort between adiposity and genotype may promote the entire spectrum of NAFLD, i.e., from steatosis to hepatic inflammation and cirrhosis (3-5). In a large cohort of adults from the Dallas Heart Study, Stender and colleagues documented that the prevalence of NAFLD spanned

from ~10% among lean individuals, who did not carry the PNPLA3 M (rs738409 C>G) variant, to ~85% among very obese patients, who were homozygous for the M variant (8). In that study, of note, adiposity remarkably magnified the effects of the M variant on the risk of developing advanced forms of NAFLD, including NASH, advanced fibrosis and cirrhosis (8). Almost identical findings were also observed for (steatogenic) alleles of GCKR (rs1260326 C>T) and TM6SF2 (rs58542926 G>A), thereby suggesting that obesity may amplify the impact of these alleles on the risk of NAFLD, probably through the alteration of their expression (8). Similar findings were also observed for children and adolescents (4). For instance, in a cohort of 514 obese children and adolescents (mean age 11.2 years, mean z-BMI 3.3), Zusi and colleagues confirmed that TM6SF2 (rs58542926), PNPLA3 (rs738409) and GCKR (rs1260326) were the most important genetic variants associated with NAFLD (as detected by ultrasonography) (9). In addition, in that study, ELOVL2 (rs2236212 G>C) variant was also independently associated with the presence of NAFLD (9). Interestingly, when the authors created a genetic risk score based on the combination of 11 genetic risk variants plus known clinical risk factors, the improvement of risk prediction for NAFLD was nearly 5%, when compared to risk prediction based on clinical risk factors alone (9). This significant, albeit slightly, improvement in the prediction of NAFLD underscores a relevant question: how many genetic factors have yet to be discovered to obtain an adequate prediction of NAFLD risk? Indeed, NAFLD is driven by multiple genetic variants (with a modest effect when considered individually) and, consequently, additional and novel strategies may be required to unravel the exact genetic architecture of the disease. In a recent genome wide association study involving both adults and children and adolescents, Namjou and colleagues found that post-GWAS association analysis combined with enrichment analysis identified novel genetic contributors for NAFLD (10). This is consistent with the missing heritability problem in which, actually, genetic associations discovered (so far) account merely for a fraction of trait heritability.

Along with increased adiposity, it is important to note that other environmental factors, such as dietary factors (fructose intake) and lack of physical activity, may trigger the expression of specific genes implicated in the development and progression of NAFLD (4,5).

Rare genetic mutations that modify the function of specific proteins implicated in the pathogenesis of NAFLD appears to be also involved in the susceptibility of advanced forms of NAFLD (4,5). Mutations in apolipoprotein B, for instance, may concur to the NAFLD progression by leading lipid compartmentalization in hepatocytes (4). Mutations in the telomerase reverse transcriptase gene (TERT), causing telomere shortening and cell senescence, seem also to be linked to progression of NAFLD (4).

To date, although these data are intriguing and fascinating, the US and the European guidelines for NAFLD do not support the use of specific genetic scores for the prediction of NAFLD risk in adults and in children or adolescents (11,12). That said, along with other authors (3-6), we believe that the potential future availability of new genetic loci of predisposition to NAFLD may improve the role of genetics in risk prediction for NAFLD and that the progressive reduction in the costs of genotyping will promote the use of specific genetic scores in clinical practice. In fact, seeing that NAFLD is a common disorder worldwide and is associated with important hepatic and extra-hepatic complications, the identification of individuals at higher risk of developing NAFLD on the basis of their genetic risk score may help clinicians to assess the patient's unique risk of NAFLD and, consequently, to undertake personalized initiatives for its diagnosis and treatment (5). At present, the search for novel therapeutic agents for NAFLD is targeting many pathophysiological processes, ranging from hepatic steatosis to NASH and fibrosis (13). Specifically, the main pathophysiological processes to target in the treatment of NAFLD are insulin resistance, lipid metabolism, inflammation, oxidative stress, apoptosis and fibrogenesis (13). Ideally, in order to individualize treatment decisions, we may have the possibility to incorporate data from genes that regulate the aforementioned mechanisms along with lifestyle and environmental data (14). Indeed, this is not a revolutionary concept, but the technological advancements have provided the excitement that a new sunrise in precision medicine is coming (14). In the years to come, it could happen even for patients with NAFLD (4,5). We are at an early stage in the understanding of how genetic information could be used in order to identify specific patients for treatment response (4,5,14). Surely, the improvement of our algorithms adding predictive genetic variation and biomarkers for drug responsiveness and the risk of complications should strength our capacity to modify NAFLD care. The dawn of a new era for NAFLD.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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