Snapshots series

Personalized Medicine in Nonalcoholic Fatty Liver Disease

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**Abbreviations**

eQTL, expression quantitative trait loci

*GCKR*, glucokinase regulator

*HSD17B13*, hydroxysteroid 17-beta dehydrogenase 13

*MBOAT7*, membrane bound O-acyltransferase domain containing 7

NAFLD, nonalcoholic fatty liver disease

NASH, nonalcoholic steatohepatitis

*PNPLA3*, patatin-like phospholipase domain containing 3

PRS, polygenic risk score

*TM6SF2*, transmembrane 6 superfamily member 2

**Key words:** NAFLD; NASH; genetics; *PNPLA3*; polygenic risk scores
The keystones of precision medicine in complex traits are to predict the onset and progression of the disease. While there are different paths toward precision medicine, genetic assessment may be among the top strategies. The current knowledge of the complete human genome sequence and the availability of next-generation sequencing technologies to decipher individual patients' genetic make-up also invite fully integrated genomic medicine. Therefore, patients may be classified into high or low risk for disease onset or severity, and therapeutic interventions can be personalized. Most importantly, precision medicine must ensure health benefits across geography, ethnicity, age, and gender.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease whose prevalence has reached global epidemic proportions in adults and children. Once diagnosed, treatment of NAFLD is complex and often requires pharmacological intervention to treat the liver disease and its associated risk factors, such as obesity, arterial hypertension, insulin resistance, and abnormal circulating lipid profiles. Hence, in this complex scenario, NAFLD presents myriad challenges to physicians, researchers, and patients.

With the advances in the genetic knowledge of NAFLD and NASH, it becomes possible to use this information for clinical applications. For example, genetic data could be leveraged to identify...
individuals at risk of NAFLD or estimate the risk of severe histological outcomes, including NASH-fibrosis, cirrhosis, and hepatocellular carcinoma. The biological information gained through the years should be integrated with clinical data and translated into efficient, cost-effective, and reliable decision-making. This bioinformatics integration increases efficiency in the clinical setting and improves diagnosis, ultimately facilitating disease monitoring and therapeutics and saving on health care costs.

Major NAFLD-associated gene variants function in metabolic pathways, including substrate delivery for de novo lipogenesis, mitochondrial energy utilization, lipid droplet assembly, lipolytic catabolism, and fatty acid compartmentalization. However, variants in some genes, for example, rs738409 in PNPLA3 and rs58542926 in TM6SF2, present pleiotropic associations that can even explain some systemic effects on emerging diseases, such as COVID-19. Pleiotropy analysis in a recent genome-wide association study of unexplained chronic alanine aminotransferase elevation as a proxy for NAFLD revealed that several replicated variants were jointly associated with metabolic and/or inflammatory traits revealing a complex model of genetic architecture.

In addition, genetic knowledge integration, data modeling, and analysis are vital processes at the interface with drug discovery. However, drug discovery and precision medicine require a complete understanding of new technologies and gene and protein biology of the selected target. A unique approach to advancing in identifying genetic factors associated with NAFLD is, for instance, the discovery of disease-specific expression quantitative trait loci (eQTL). This approach showed that the rs2291702 variant located in AGXT2 (Alanine-Glyoxylate Aminotransferase 2) gene protects against liver fibrosis in a genotype-dependent manner with the potential for therapeutic interventions.

Despite NAFLD heritability is ~50%, as in other complex diseases, a significant proportion of the disease burden remains explained; the so-called "the missing heritability". The concept of the missing heritability includes not only genetic and epigenetic modifiers but the interaction with environmental exposure and diet as well as highly interconnected and dynamic factors such as the liver microbiome. Some examples of the poorly explored heritability estimates of NAFLD and NASH that explain the disease variance are rare variants—which probably would have substantial
effect/s on the phenotype, the exploration of structural variation, the assessment of interaction among
the involved loci—also known as epistasis, and the genetic diversity of the mitochondrial DNA, among
many other examples ⁵. Recently, a human study demonstrated that variants influencing the risk/protection against NAFLD-
histological severity (PNPLA3-rs738409, TM6SF2-rs58542926, MBOAT7-rs641738, and HSD17B13-
rs72613567) and a variant influencing macronutrient intake (FGF21-rs838133) may influence the
liver microbial DNA composition ¹³. The significant variants' combined effect associated with a
polygenic risk score (PRS) suggested a link between the liver metataxonomic profile, host genetics,
and cardiovascular risk ¹³.

The ultimate goal of precision medicine is to estimate a given patient susceptibility risk to developing
a particular disease. In this regard, PRS are valuable instruments for stratifying the population risk
according to the individual genetic profile. However, challenges include the missing heritability,
discovery of rare variants ¹⁴, ¹⁵, and reproducibility of GWAS findings in diverse populations ¹. On the
other hand, the advantages are the potentiality of distinguishing patients with high or low risk of
severe disease ¹. Although, outside of the focus of this snapshot, advances in transcriptomics,
proteomics, and metabolomics integrated with genomics in a multi-omics approach ¹⁶ are presenting
us a fascinating scenario for the personalized medicine of NAFLD and comorbidities

In conclusion, the newly acquired genetic information should be used to improve the understanding of
disease pathogenesis, which may allow the early identification of at-risk patients, who would benefit
most from early treatment. Potential avenues for future research should focus on prevention,
surveillance, and prognosis assessment of NAFLD and NASH. The ultimate role of precision therapy
relies on defining appropriate prediction strategies for implementing patient-based therapies.

Conflicts of Interest

The authors have no conflicts to disclose

Authors' contribution

C.J.P Concept of the work, manuscript writing and approval. S.S. Concept of the work, manuscript
writing and approval.
REFERENCES


