Precision Medicine in NAFLD: Are We There Yet?

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PRESENTING at an interactive session entitled 'Precision medicine for the management of NAFLD - Are we there yet?' at The Digital International Liver Congress 2020 on 29th August 2020, a number of experts shared their insights into current genetic understandings of nonalcoholic fatty liver disease (NAFLD) and how heterogeneity of phenotypes provides opportunities for precision medicine approaches.

PRECISION MEDICINE

In his opening presentation, Dr Salvatore Petta, University of Palermo, Palermo, Italy, discussed the concept of precision medicine and the features of NAFLD that make it an excellent candidate for a precision medicine approach. "We can define precision medicine as treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations," he explained. Precision medicine approaches rely upon the presence of heterogeneous disease for targeted, individualised care; diagnostic tests that allow for refined disease classification or prognostication to create subtypes within the same disease; and therapeutic targets that allow for specific treatments of different phenotypes of the same disease.

NAFLD is a heterogeneous disease in that prevalence of progressive complications, including fibrosis and hepatocellular carcinoma (HCC), is varied, and associated comorbid conditions also vary across affected individuals. The phenotypes of NAFLD, according to Dr Petta, include multiple types of subgroups: metabolic syndrome-associated NAFLD, in patients with associated obesity and Type 2 diabetes mellitus (T2DM); lean NAFLD in patients without other features of obesity; lipid disorder-associated NAFLD in patients with increased rates of cardiovascular disease; patients who progress rapidly versus those who are slow to progress; and those patients with cardiovascular or extrahepatic complications of NAFLD versus those with hepatic complications. This variation in phenotypic expression allows for subgroup typing of individuals, which is of great importance in the development and application of precision medicine; however, diagnostic capabilities are not yet developed to be able to completely classify these subtypes.

Prognostic variation between subgroups in NAFLD allows for some classification of these groups and has led to the identification of some genetic markers and variants. Dr Petta highlighted that comorbid metabolic factors can

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discriminate fibrosis risk in known NAFLD, with arterial hypertension, a definite risk factor for rapid progression of liver fibrosis. The presence of T2DM predicts an increased risk of liver fibrosis over time, but the metabolic risk factors of T2DM, hypertension, dyslipidaemia, and obesity have a combined impact on the time to development of cirrhosis greater than each of their cumulative impacts on cirrhosis risk. However, the most specific classifications currently available, with the greatest hope for development of precision medicine for NAFLD, are the identified genetic variants associated with different NAFLD phenotypes.

GENETIC VARIANTS

In the second presentation, Prof Elizabeth Speliotes, University of Michigan, Ann Arbor, Michigan, USA, outlined the current understanding of genetic variants across heterogeneous phenotypes of NAFLD. In seeking to better understand this heterogeneity, genome-wide association studies have identified seven loci that account for approximately 15% of the heritability of NAFLD. Variants across these gene loci have differing effects on heritability or liver disease phenotypes and have differing associations with markers of dyslipidaemia and metabolic syndrome. Prof Speliotes highlighted the research and clinical value of these findings: "This is actually very exciting because it shows that genetics can dissociate epidemiologically correlated traits," which can then potentially be used as markers to identify subgroups of NAFLD for prognostic understanding and therapeutic targets: the basis of precision medicine.

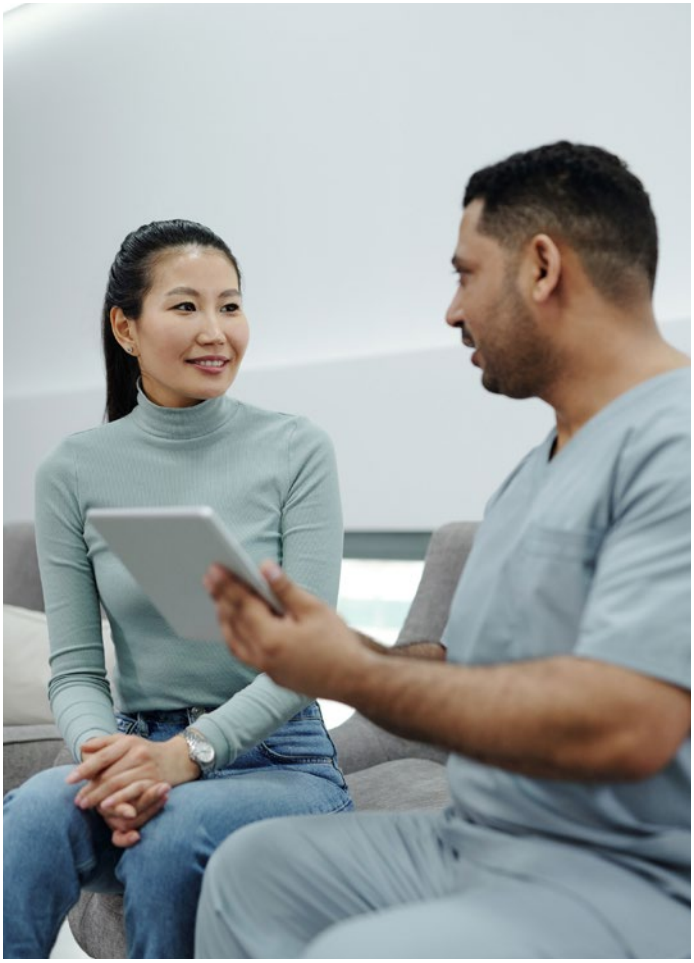
To assess the value of testing for genetic variants to identify these subgroup patients, Prof Speliotes described population studies of thousands of patients that considered the interaction of these genetic variants with environmental factors. These studies found that the genetic variant PNPLA3 I148M, when combined with elevated serum insulin, glucose, triglycerides, and BMI, multiplied the risk of developing hepatic steatosis beyond the cumulative risk of each individual risk factor. A further study assessed the value of intervening in these genetically at-risk subgroups by comparing the impact of lowering insulin resistance; it found a greater reduction in risk of NAFLD following lowering of insulin resistance in those patients with the PNPLA3 genotype compared to those without the genetic variant. This magnified benefit of intervention was also seen in shorter-term interventional studies, including a study where patients with the higher risk genetic variant lost a greater amount of liver fat during a 6-day hypocaloric diet compared to those without the genetic variant, even with identical weight loss.

LIVER LIPIDOME

In her closing presentation, Prof Hannele Yki-Järvinen, University of Helsinki, Helsinki, Finland discussed the genetic variants of phenotypic subtypes of NAFLD, and how they impact lipid metabolism and expression in the liver (i.e., the liver lipidome). Multiple genetic variants predispose to progressive NAFLD, but several other genetic variants protect against progression of steatosis to more advanced forms of liver disease, or protect against development of cardiovascular disease or T2DM. To illustrate the impact of genetic variants on lipid metabolism in NAFLD, Prof Yki-Järvinen described her research identifying hepatic lipid expression by genetic variant subtype. "To our surprise, the human liver lipidome was markedly different in metabolic NAFLD and PNPLA3 NAFLD," she explained. She found that metabolic phenotypes had a predominance of saturated or monounsaturated fatty acids, whilst those individuals with PNPLA3 NAFLD had almost no triglycerides and a greater predominance of highly polyunsaturated fatty acids. Ceramides, which are known to contribute to insulin resistance, T2DM, and cardiovascular disease, were found to be markedly increased in metabolic NAFLD but not in those carrying

the PNPLA3 gene variant, which Prof Yki-Järvinen indicated is potentially the reason for the association of metabolic NAFLD with these comorbidities but not of PNPLA3 NAFLD.

In protective genetic variants in NAFLD, those that protect against the development of cardiovascular disease, T2DM, or liver malignancy, there were also subtype-specific alterations in the liver lipidome. HSD17B13, a lipid droplet protein expressed in the liver, has a protective variant HSD17B13 rs72613567 that decreases the risk of alcoholic and nonalcoholic cirrhosis, fibrosis, and HCC in NAFLD, but does not affect steatosis. The lipidome in this variant was associated with increased liver phosphatidylcholines and phosphatidylethanolamines. MARC1, an enzyme of unknown function located in the outer mitochondrial membrane, has a protective variant MARC1 rs2642438 that shields against steatosis and cirrhosis and is associated with decreased low-density lipid cholesterol. Study of the lipidome of this variant found it to be associated with increased hepatic phosphatidylcholines, and less inflammation and fibrosis. The significance and underlying mechanism of the changes in lipidome with these protective variants, particularly the increase in hepatic phosphatidylcholines, is currently being investigated.



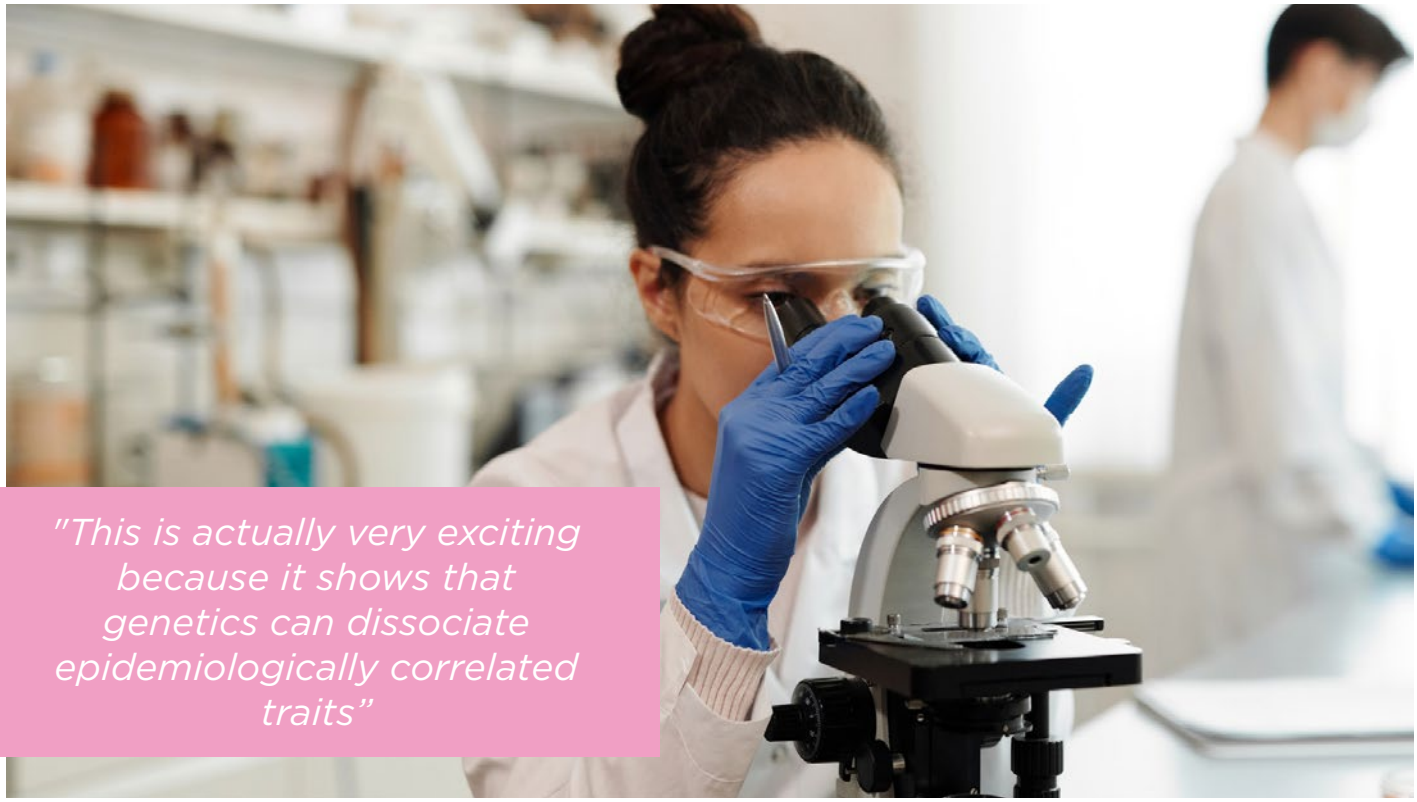
ROLE OF EPIGENETICS

Epigenetic modifications also influence the heterogeneity of phenotypes in NAFLD, as outlined by Dr Sookoian, University of Buenos Aires, Buenos Aires, Argentina, in her presentation. "Epigenetics is the interface between the environment, fetal life, and the genome," clarified Dr Sookoian, before briefly providing an overview of the three major processes of epigenetics that may play a role in NAFLD phenotypes. Gene methylation is usually associated with gene repression and usually occurs at the gene promoter region. Histone modification is generally associated with gene expression and involves many post-translational modifications. Another mechanism of epigenetics is noncoding RNA-mediated gene silencing, which involves regulation of chromatin structure, co-operation with methylases, and effects RNA stability.

Epigenetic changes found in NAFLD include hypermethylation of the promoter of PGC1α, a master metabolic regulator, in patients with NAFLD (47.9% of alleles methylated), which is associated with decreased mitochondrial copy number and increased insulin resistance. In advanced NAFLD, epigenetic changes are found in tissue repair genes (hypomethylated and overexpressed), which leads to the accumulation of scar tissue, and in metabolic genes (hypermethylated and under-expressed), which leads to metabolic dysregulation.

FUTURE APPLICATIONS AND RESEARCH DIRECTIONS

Although progress in refined diagnostic testing and further scientific understanding of the pathophysiology of genetic variant-specific subtypes is needed, the presenters highlighted a few approaches for precision medicine in NAFLD already underway. Studies of environmental modifications in PNPLA3 NAFLD suggest that dietary or surgical interventions to reverse obesity will have a more pronounced reduction in risk of NAFLD development or progression in individuals carrying this variant. Another



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potential strategy in this subgroup is to directly address the genetic variant itself. PNPLA3 I148M is a 'gain-of-function' variant, Prof Speliotes explained, where the presence of the variant gives a new deleterious phenotype, while the absence of the variant has no known effect. It is thought that the action of this variant reduces triglyceride hydrolysis in lipid droplets in cells. A study in mice using antisense oligonucleotides for gene editing of this variant found a reduction in steatosis and fibrosis, and protection against diet-induced obesity. Prof Speliotes discussed a case example of gene editing in sickle cell disease as a suggestion that gene editing for NAFLD could be a future valuable intervention. For the other genetic variants, the complex protective interplay with other conditions including cardiovascular disease, metabolic syndrome, and diabetes, mean that more context-specific considerations are needed, and further research is required before genotype-specific recommendations can be developed.

Epigenetic modifications can also potentially be utilised in the management of NAFLD. Dr Sookoian discussed a study of patients following bariatric surgery that found that their methylation pattern demonstrated epigenetic remodelling post-treatment. This suggests that epigenetic changes are potentially modifiable or partially reversible. Another study of a biomarker present in NAFLD, miR-122, found it to be upregulated in the circulation and downregulated within the liver of patients with NAFLD; miR-122 was found to have a regulatory role in serum levels of alanine (ALT), and downregulation of the miR-122 gene was associated with loss of the hepatic phenotype in NAFLD and features associated with cancer. Dr Sookoian discussed that targeted downregulation of this noncoding microRNA could be a potential future target of precision medicine, before discussing other identified noncoding RNA and epigenetic components with associations to NAFLD subtypes, prognosis, and complications.

Prof Speliotes expects that NAFLD will be the leading cause of liver disease worldwide "within a year or so," highlighting that this means it is "one of the biggest unmet medical needs of our time" because of the lack of effective medical treatments currently available. Given this unavailability of successful treatment and the growing prevalence, improved understanding and rapid translation to clinical practice is a priority. In closing the session, chair Prof Stefano Romeo, University of Gothenburg, Gothenburg, Sweden, articulated the value of addressing progress in precision medicine in NAFLD: "I think this is the key question for the next decade: on whether we'll be able to implement precision diagnosis and therapy for our patients."