MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

Section Editor: Stephen A. Harrison, MD

Current Status of Genetics and Polygenic Risk Scores in Metabolic Dysfunction-Associated Steatohepatitis

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G&H What are the main risk alleles and protective variants for metabolic dysfunction-associated steatohepatitis?

NC There are a number of risk alleles, of which the most important is the *PNPLA3* variant. Also important is the *TM6SF2* variant. If patients have mutant alleles of these genes, they are more likely to have metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), and related fibrosis and cirrhosis.

In contrast, the variants in *HSD17B13* are protective. Patients with an alternate allele of this gene are less likely to have MASH fibrosis and cirrhosis. Additionally, Dr Stefano Romeo has described variants in *PSD3* that appear to be protective, although other investigators have not been able to reproduce that finding. Interestingly, a recent study has observed that the protection offered by very rare variants in *CIDEB* exceeds that of *HSD17B13* variants.

> Generally speaking, published studies have shown that heritability plays a more important role in MASLD and MASH in children than in adults.

G&H Currently, what is the prevalence of MASH-specific genetic mutations among different ethnic and racial populations?

NC The *PNPLA3* variant has been studied the most and varies in different races and ethnicities. Hispanic individuals residing in the United States and Mexico have very high prevalence of the *PNPLA3* G allele, which is the risk allele for MASLD and MASH. Among Hispanic individuals, the country of origin appears to make a difference; for example, those of Mexican origin appear to have higher prevalence of the risk allele than those of Caribbean origin. Individuals with African ancestry or non-Hispanic Black individuals appear to have much lower prevalence of the *PNPLA3* G allele.

On the other hand, not as much is known in terms of *HSD17B13* variants and race/ethnic distribution. Approximately 7% of European White individuals carry *TM6SF2* variants, which, I believe, are rare in African Americans and non-Hispanic Blacks.

G&H Have any specific genetic variants been uncovered for lean MASH or MASLD?

NC *PNPLA3*-associated MASLD and MASH were originally thought to be unrelated to higher body mass index (BMI) or hypertriglyceridemia. The thinking was that lean MASH or MASH in nondiabetics was more likely to be driven by *PNPLA3,* but I do not think subsequent

published data entirely support this notion. I think genetic variants associated with MASLD and MASH in the general population remain important for lean individuals with these conditions.

Additionally, perhaps 1% to 4% of patients with MASLD or MASH have variants in apolipoprotein B (APOB), which can lead to familial hypobetalipoproteinemia. These individuals are more likely to have low circulating low-density lipoprotein (LDL) cholesterol, whereas individuals with *TM6SF2* variants are more likely to have high LDL cholesterol. However, individuals can have low LDL and not have APOB, or they may have high LDL and not have *TM6SF2* variants.

G&H Is genetics more important than the environment in MASH?

NC MASLD and associated fibrosis are heritable. About 50% of fibrosis is thought to have a heritable component. Generally speaking, published studies have shown that heritability plays a more important role in MASLD and MASH in children than in adults. In other words, genetic variants play a more important role in pediatric MASH than the environment does. When it comes to adult MASH, both genetics and environmental factors play an important role and interplay with each other. For example, if a patient carrying a *PNPLA3* G allele is also a diabetic, their risk of advanced fibrosis is quite high and their risk of adverse liver-related outcomes is also significantly higher.

> … although these polygenic risk scores look promising, *PNPLA3* alone appears to account for much of their relationship with hepatic histology and advanced fibrosis.

G&H Have any polygenic risk scores demonstrated value in MASH?

NC There are a number of polygenic risk scores in this space, including some that my colleagues and I have been part of. A 17-gene polygenic risk score recently published in *Nature Genetics* by Chen and colleagues strongly predicts the risk for hepatic steatosis. Our recent work has shown that this score is also significantly associated with hepatic histology and advanced fibrosis. A polygenic risk score that includes only 3 variants in *PNPLA3*, *TM6SF2*, and *HSD17B13* has shown strong association with hepatic histology and advanced fibrosis. My colleagues and I have submitted an abstract for the upcoming American Association for the Study of Liver Diseases meeting showing that although these polygenic risk scores look promising, *PNPLA3* alone appears to account for much of their relationship with hepatic histology and advanced fibrosis. For example, if the polygenic risk score by Chen and colleagues is recalculated without *PNPLA3*, its significance drops meaningfully. Thus, it appears that the most important component of the score is *PNPLA3*.

G&H In what phase of development are these scores?

NC They are still in early investigative phases; none are being used yet in clinical practice. At the moment, researchers are trying to validate what has been published in the literature. Moving forward, there will likely be efforts to try to improve some of the existing polygenic risk scores. There will also be debate on their overall importance. It is agreed that patients who have MASH with stage 2 or higher fibrosis are at high risk for developing cirrhosis and its complications. Biopsy has traditionally been considered the gold standard to identify the stage of fibrosis, but the procedure has a number of limitations. Instead of using a biopsy, could a polygenic risk score identify patients at high risk for severe disease such that only those with high scores could be treated? That is certainly a possibility and why these scores are being developed. However, there is a long way to go before we can clinically apply polygenic risk scores for disease stratification and personalized treatment or to identify patients who will benefit from screening for liver cancer and varices.

G&H How have advances in MASH genetics helped identify targets for drug development?

NC Genomic discoveries have very quickly evolved into therapeutic targets in the MASH space. There are ongoing clinical trials with drugs targeting *PNPLA3* as well as *HSD17B13*. However, these studies are in early-phase development; none have crossed phase 2 yet. There are also preclinical and phase 1 studies interrogating other genetic variants as therapeutic targets. Identifying a specific genetic defect and then administering a therapy targeting it offers a personalized approach for treating MASH and fibrosis.

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G&H What future research is needed involving genetics and polygenic risk scores in MASH?

NC Precision genomics in MASH is in its infancy. Its goal is to facilitate disease stratification and identification of patients at risk as well as identification of patients who are good candidates for a particular therapy. Several steps are involved in applying clinical genomics to patient care. It is important to have buy-in from multiple stakeholders and clearly understand where we want to take the field and then work backward to determine the evidence needed and milestones to achieve. Not much research has been performed yet in this area as well as on provider and patient awareness or reimbursement. Data are needed to convince payers that covering genetic testing is a positive value proposition from a health care utilization standpoint. I suspect that the vast majority of providers do not fully understand the components of heritability and its impact on developing MASLD or on disease progression; however, not a lot of work has been done in this space. At the present time, few hepatology groups in the country are performing routine *PNPLA3* testing as part of clinical care. For the most part, the genetic architecture of MASLD and MASH patients who are being clinically cared for throughout the country is not known. The field has to evolve and figure out how to apply this knowledge to patient care. If *PNPLA3*- or *HSD17B13*-based therapies prove to be effective, more groups will start testing their patients.

Further research is also needed to better understand the interplay between genetic variants and environmental factors such as BMI, type 2 diabetes, and alcohol consumption and the risk for disease progression. More research is also needed to understand the interplay between genetic risks of MASLD and those of its risk factors such as type 2 diabetes and obesity. For example, if a patient with a top-quartile polygenic risk score for type 2 diabetes also carries the *PNPLA3* G allele, are they at higher risk for MASH and disease progression?

Disclosures

Dr Chalasani has consulting agreements and research grant support from several pharmaceutical companies, but those relationships are not related to this column.

Suggested Reading

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