NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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Genetics of Nonalcoholic Steatohepatitis

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G&H What are the main genes involved with nonalcoholic steatohepatitis?

AS There are a growing number of genes that have been linked both to the development of the disease and to its progression. Best established is the *PNPLA3* gene, where a mutation at position 148 in the gene has been linked to developing more aggressive steatohepatitis, more fat, more inflammation and injury, more scarring, and greater risks of cirrhosis and hepatocellular carcinoma. It turns out that this gene is not only relevant for nonalcoholic steatohepatitis (NASH), but also for several other types of liver diseases, such as hepatitis C and alcoholic liver disease.

The second major gene that is receiving a lot of attention is the 17 beta-hydroxysteroid dehydrogenase gene mutation (*HSD17B13*), where, through alternative splicing, there is a variant that is protective against NASH. Interestingly, having the *HSD17B13* variant appeared to offset some of the injurious aspects of the *PNPLA3* gene in people with both gene variants. This is clearly an emerging and important aspect of how NASH develops and progresses.

G&H Can genetic mutations act synergistically to promote disease progression?

AS Certainly. The *TM6SF2* gene mutation promotes disease progression, as does the *PNPLA3* mutation. There are other gene mutations that are linked to metabolic disease, and it would make sense that the more of these a person has, the more likely it is that disease will progress. The best way to determine this quantitatively is by developing a polygenic risk score. This score takes the presence of all of the key alleles and then determines a composite risk of progression that includes both the positive genes and the negative genes—ie, the genes that are pushing the disease toward cirrhosis and the genes that are trying to help restore normalcy.

There are many areas such as diabetes and hypertension for which there are well-established polygenic risk scores. However, such a score has not yet been validated for NASH. The difficulty with developing a robust score for NASH is that to include rare variants, tens of thousands of patients are needed. That data will eventually come, but presently the data sets include only thousands of patients.

G&H Can genetics in addition to demographic information help identify patients at increased risk of disease progression?

AS That is the ideal goal because disease progression is related to gene-environment interactions. However, we have not come to a point yet where a polygenic risk score has been validated to identify who currently has significant disease as well as determine how much of an increase in risk is conferred by a given rise in the score. That is where the field is headed.

G&H What is the prevalence of NASH-specific genetic mutations among different ethnic populations?

AS Each mutation is different. Best studied is the *PNPLA3* mutation, which is seen in approximately 15% of the general population, up to 50% of Hispanic individuals, and a much lower number of African Americans. *HSD17B13* is much more of a rare variant, so the prevalence is not quite as high. Some of the other rare variants, such as the *TM6SF2* mutation, are only identified through exome sequencing, and are, thus, extremely low in prevalence.

G&H Does genetics then explain why African Americans have less NASH than Hispanics, whites, and Asians?

AS Genes are certainly at least a partial explanation, although I am not certain whether they explain the difference in its entirety. As mentioned, the *PNPLA3* mutation has a very low prevalence in African Americans compared to Hispanics (who have the highest prevalence) and whites (who have a prevalence somewhere in the middle).

G&H Is genetics more important than environment in NASH?

AS Genetics does not explain everything in NASH, just like, on the other hand, it is not completely irrelevant. The truth, as with most things in life, lies in the middle. NASH is related to gene-environment interactions. Because of the diversity of the genes, pathways, and environmental influences (eg, exercise, food, microbiome) that are involved, there is tremendous heterogeneity from one person to the next in terms of disease drivers. NASH is a clinical syndrome that can develop through a multitude of pathways. Until we understand the diversity of the pathways by which the disease is produced and progresses and we can identify which pathways are relevant in a patient at a given point in time, we will not be able to develop highly effective treatments. NASH is not a one-size-fits-all disease.

G&H Will certain genetic mutations likely prevent response to therapy?

AS Yes. For example, when fish oil was given to treat fatty liver disease, having the *PNPLA3* mutation worked against the treatment, which was not shown to have an overall benefit in clinical trials. This mutation causes significant depletion of unsaturated fatty acids and transfers them onto triglycerides, which reduces the availability of polyunsaturated fatty acids (PUFAs), especially n3 PUFAs, for their normal anti-inflammatory functions. Clearly, more work is needed in the area of pharmacogenomics to better understand how to use genetic information to direct therapeutics.

G&H On the other hand, will certain genetic mutations likely improve response to therapy?

AS Theoretically, yes, based on the mechanism of action and where different drugs are being targeted. The *PNPLA3* gene is being looked at as a therapeutic target because increased gene expression has been shown to be associated with negative effects. There are now efforts to reduce the level of expression of this gene to try to reverse liver disease. Similarly, there are early efforts in planning to study the *HSD17B13* gene. Thus, the genes themselves can be therapeutic targets. In addition, there are several ongoing clinical trials that are actively looking to see whether there is a pharmacogenomic element in which having specific genes can tell doctors whether a patient will respond to a particular type of treatment, which would enable precision medicine to become a reality.

Ultimately, we will need polygenic risk scores, and we will need new paradigms to connect genes to the transcriptome and metabolome to be able to identify subsets of people who have specific pathways and disease drivers, which will allow us to target these patients with specific treatments. As in oncology, we will eventually need to know which mechanisms in a given individual are relevant at a point in time and how they can be leveraged for treatment. Instead of giving one drug to hundreds of patients and hoping some of them will benefit, we will be able to match the drug and the patient to each other.

G&H Could you provide details on any of the therapeutic research currently underway?

AS There are antisense approaches being developed to directly silence the *PNPLA3* gene. Similarly, there are approaches being developed to target and shut down the wild-type *HSD* gene, and there are other approaches being planned to enhance the expression of the mutant splice variant of the *HSD17B13* gene, which essentially is protective. These approaches are still in the planning stages. Animal research, however, has shown that NASH accelerates with the expression of *PNPLA3* and that reducing the expression of this gene reverses the phenotype even if the animal remains on a high-fat diet.

G&H Are there any other aspects of the genetics of NASH that require further research?

AS Genetics is important in the context of NASH, and not just in terms of NASH-specific genes. In the development of obesity, the principal risk factor for NASH, if a person eats too much and does not burn it off, a fat

load is released to the liver. When this fat load stresses the right genetic milieu, it leads to cell stress, which injures and kills liver cells, resulting in inflammation. If this was a one-time event, the inflammation would come in, clean out the dead cells, and then leave, and the situation would normalize. However, when there is ongoing obesity and excess metabolites are being delivered to the liver, the cell stress does not stop, resulting in perpetuated inflammation. This triggers the scarring response, which is nature's way of walling off inflammatory activity, and leads to progressive scarring and then cirrhosis. At each step, response to the same trigger and degree of injury may vary based on the person's genetic composition. In my view, our understanding of the genetic underpinning of NASH and its implications is still not complete. There is a lot more to be done to understand genetics at every stage of the disease and what roles genetics plays.

For example, for fibrosis, which is one of the later consequences of the disease, there are genes that modify the fibrogenic drive or the aggressiveness with which scar tissue can develop. Some people with NASH are known as rapid progressors. This could be due to altered metabolic milieu and increased injury to the liver, or it could be because these individuals are genetically predisposed to scar more aggressively. I think there are opportunities there for therapeutic intervention. Most of the therapies that are being developed are at the metabolic end, which is the upstream root cause of the liver disease. Having said that, thus far, the treatments that have targeted fibrosis have not worked very well. None of them have been consistently effective. That is an area where there is a lot of preclinical research currently ongoing, but we are far away from translation into human study.

Disclosures

Dr Sanyal is president of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, Inversago, and Galmed. He has served as a consultant to AstraZeneca, Nitto Denko, Conatus, Nimbus, Salix, Tobira, Takeda, Janssen, Gilead, Terns, Bird Rock Bio, Merck, Valeant, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, HemoShear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exalenz, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Synlogic, Afimmune, ChemomAb, Zydus, Nordic Bioscience, Albireo, Prosciento, and Surrozen. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers Squibb, Shire, Intercept, Merck, AstraZeneca, Mallinckrodt, Cumberland, and Novartis. He receives royalties from Elsevier and UpToDate.

Suggested Reading

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