Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.008.

References

[1] Hakim A, Zhang X, DeLisle A, Oral EA, Dykas D, Drzewiecki K, et al. Clinical utility of genomic analysis in adults with idiopathic liver disease. J Hepatol 2019;70:1214–1221.

[2] Pinto EVF, Lazaridis KN. Individualized medicine comes to the liver clinic. J Hepatol 2019;70:1057–1059.

[3] Pelusi S, Baselli G, Pietrelli A, Dongiovanni P, Donati B, McCain MV, et al. Rare pathogenic variants predispose to hepatocellular carcinoma in nonalcoholic fatty liver disease. Sci Rep 2019;9:3682.

[4] Noto D, Cefalu AB, Cannizzaro A, Mina M, Fayer F, Valenti V, et al. Familial hypobetalipoproteinemia due to apolipoprotein B R463W mutation causes intestinal fat accumulation and low postprandial lipemia. Atherosclerosis 2009;206:193–198.

[5] Peloso GM, Nomura A, Khera AV, Chaffin M, Won HH, Ardissino D, et al. Rare protein-truncating variants in APOB, lower low-density lipoprotein cholesterol, and protection against coronary heart disease. Circ Genom Precis Med 2019;12 e002376.

[6] Youssefian L, Vahidnezhad H, Saeidian AH, Pajouhanfar S, Sotoudeh S, Mansouri P, et al. Inherited non-alcoholic fatty liver disease and dyslipidemia due to monoallelic ABHD5 mutations. J Hepatol 2019;71:366–370.

[7] Di Filippo M, Moulin P, Roy P, Samson-Bouma ME, Collardeau-Frachon S, Chebel-Dumont S, et al. Homozygous MTTP and APOB mutations may lead to hepatic steatosis and fibrosis despite metabolic differences in congenital hypocholesterolemia. J Hepatol 2014;61:891–902.

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Reply to: "Whole exome sequencing for personalized hepatology: Expanding applications in adults and challenges"

Exome sequencing advances precision medicine in adult hepatology

To the Editor:

It is with enthusiasm that we read the letter by Dr Valenti *et al.* entitled "Whole exome sequencing for personalized hepatology: expanding applications in adults and challenges" on the application of whole exome sequencing (WES) in the evaluation of 201 patients with advanced liver fibrosis attributed to non-alcoholic fatty liver disease (NAFLD), including individuals with hepatocellular carcinoma.

In alignment with our group's experience,[1] the authors identified a Mendelian disease in a significant subset of patients (11%), which had been undiagnosed until genomic analysis was performed in adulthood. Interestingly, the authors found that approximately 7.5% of their cohort harbor heterozygous deleterious variants in apolipoprotein B encoded by *APOB*. In order to validate the genetic findings in these patients, the authors assessed the patients' lipid profiles and found that they were consistent with the genotype, thereby uncovering the diagnosis of hypobetalipoproteinemia in 15 of these patients. This study illustrates the relevance of incorporating a forum such as Genome Rounds, where genetic findings are discussed and integrated with phenotypic features. It is important to recognize that a genetic diagnosis alone does not establish a definitive diagnosis unless supported by clinical, laboratory, imaging and/or histological findings.[1,2] Specifically, in patients with liver steatosis and rare heterozygous variants predicted to be deleterious in *APOB*, a circulating lipid profile and APOB levels should be obtained to functionally validate the clinical relevance – in other words, the pathogenicity – of uncharacterized mono-allelic loss-of-function variants in this gene. Moreover, our data and the Dr Valenti *et al.*'s study underscore that WES has the highest potential to yield actionable information when integrated in the appropriate clinical context. Specifically, patients with NAFLD typically have hepatic steatosis in the context of hyperlipidemia and low high-density lipoprotein cholesterol; when this pattern deviates to hypolipidemia, it hints at a genetic defect of apolipoprotein function and the potential utility of genetic testing. It will be very interesting to see the long-term natural history of the patients in Dr Valenti's cohort, as it is likely to differ from classical NAFLD and therefore may have implications in clinical management. Ultimately, we anticipate that a genomic approach in adult hepatology will assist to inform diagnosis, prognosis and treatment across a wide spectrum of molecular liver disease subtypes.[1–3]

Financial support

S.V. is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number K08DK113109. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

S.V. wrote the first manuscript draft. A.H. and P.K.M. critically revised the draft and contributed with valuable input.

References

[1] Hakim A, Zhang X, DeLisle A, Oral EA, Dykas D, Drzewiecki K, et al. Clinical utility of genomic analysis in adults with idiopathic liver disease. J Hepatol 2019;70:1214–1221.

[2] Vilarinho S, Mistry PK. Exome sequencing in clinical hepatology. Hepatology 2019.

[3] Pinto EVF, Lazaridis KN. Individualized medicine comes to the liver clinic. J Hepatol 2019;70:1057–1059.

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