Received: 12 November 2023 | Accepted: 30 January 2024

DOI: 10.1097/HC9.0000000000000408

REVIEW

OPEN

Genetics of liver disease in adults

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Abstract

Chronic liver disease stands as a significant global health problem with an estimated 2 million annual deaths across the globe. Combining the use of next-generation sequencing technologies with evolving knowledge in the interpretation of genetic variation across the human genome is propelling our understanding, diagnosis, and management of both rare and common liver diseases. Here, we review the contribution of risk and protective alleles to common forms of liver disease, the rising number of monogenic diseases affecting the liver, and the role of somatic genetic variants in the onset and progression of oncological and non-oncological liver diseases. The incorporation of genomic information in the diagnosis and management of patients with liver disease is driving the beginning of a new era of genomics-informed clinical hepatology practice, facilitating personalized medicine, and improving patient care.

Liver disease constitutes a substantial global health burden, causing 2 million deaths each year worldwide.[1] Despite advancements in the treatment of viral hepatitis, morbidity and mortality from liver diseases continue to rise, largely due to the global obesity epidemic and the increasing incidence of metabolic dysfunction–associated steatotic liver disease (MASLD).[1] Investigation of the genetic underpinnings of chronic liver disease (CLD) has (i) identified risk and protective alleles for a variety of common liver diseases, such as MASLD; (ii) uncovered novel monogenic diseases[2]; and (iii) expanded our understanding of the contribution of somatic genetic variants to oncological and non-oncological liver disease. The intersection of genes, genomes, and liver disease is propelling our understanding of liver biology, and in turn, improving patient care. This underscores the need for incorporating training and multidisciplinary discussions on the clinical utility of genomic analysis among hepatologists and other providers caring for patients with liver disease.

RISK AND PROTECTIVE ALLELES FOR LIVER DISEASE

Similarly to other complex traits, which are influenced by interactions between common genetic variants and the environment, MASLD has also been shown to have a

Abbreviations: AAT, alpha-1-antitrypsin; AIH, autoimmune hepatitis; ALGS, Alagille syndrome; BMI, body mass index; CF, cystic fibrosis; CLD, chronic liver disease; HCA, hepatocellular adenoma; HH, hereditary hemochromatosis; MASLD, metabolic dysfunction–associated steatotic liver disease; NGS, next-generation sequencing; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; PSVD, porto-sinusoidal vascular disease; SLD, steatotic liver disease; WES, whole-exome sequencing.

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heritable component.[3–5] The genetic drivers of MASLD in the population are primarily composed of common variants with relatively small effect sizes, which have been uncovered by genome-wide association studies (Figure 1). To date, the most well-validated single nucleotide polymorphism driving hepatic steatosis is the p.I148M variant (rs738409) in *PNPLA3*.[6] This gene is upregulated after carbohydrate feeding and associates with lipid droplets.[7,8] Studies have shown that p.I148M results in triglyceride accumulation.[9,10] It has also been shown that p.I148M is associated with an increased risk of liver fibrosis and HCC.[11–14] While Hispanics have a relatively higher incidence of MASLD, African Americans have a lower incidence, mirroring the prevalence of the p.I148M genotype in these populations.[15–17] Another common variant associated with MASLD is p.P446L (rs1260326) in *GCKR*, which encodes a regulator of glucokinase.[18] This variant is thought to alter the response of glucokinase to fructose-6-phosphate, which results in continuous glucose uptake by the liver and increased de novo lipogenesis.[19,20] A less common variant, p.E167K (rs58542926) in *TM6SF2* has also repeatedly been associated with an increased risk of MASLD.[21] While its exact function is still poorly understood, it has been shown to play a role in triglyceride secretion.[22] In addition, an individual's increase in body mass index (BMI) has been shown to enhance the penetrance of a number of these risk variants, most notably p.I148M in *PNPLA3*.[12] Furthermore, genetic variants in several other genes involved in metabolic function, such as *MBOAT7*, *GPAM*, and *APOE*, have been associated with MASLD.[23–26]

Recent genome-wide association studies using whole-exome sequencing (WES) data from larger cohorts have confirmed the role of rare variants in *APOB*, *ABCB4*, *SLC30A10*, and *TM6SF2* as risk alleles

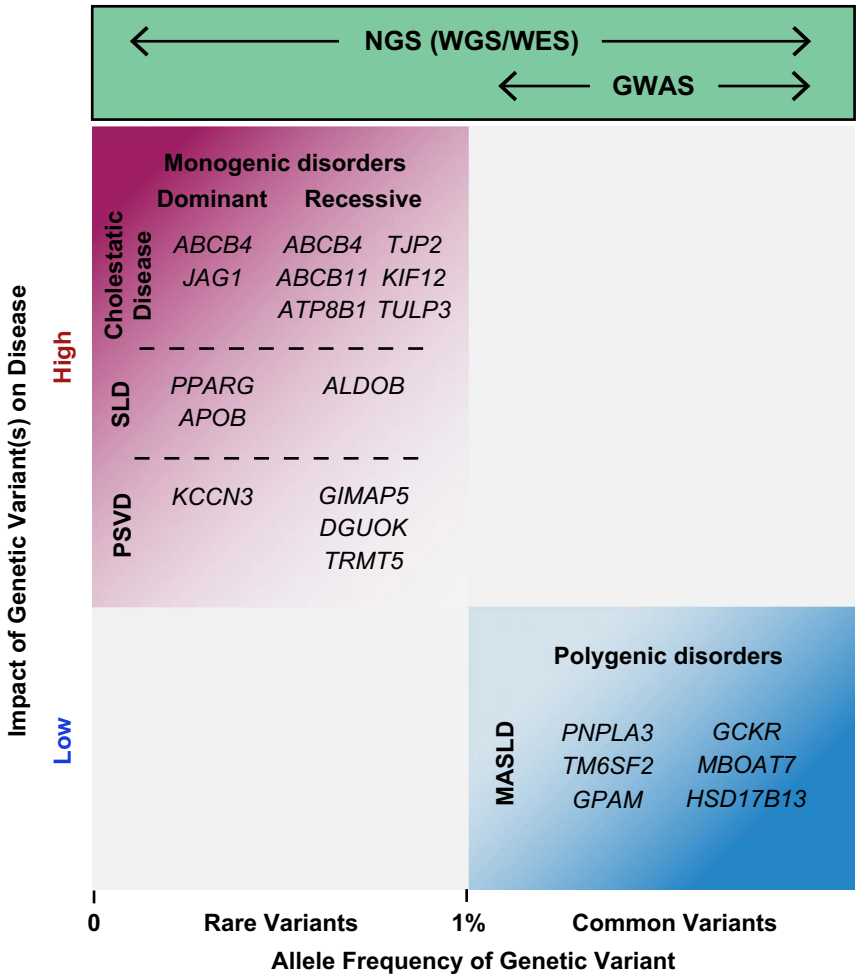

FIGURE 1 Schematic representation of the contribution of rare (minor allele frequency less than or equal to 1%) genetic variants to monogenic liver diseases, and more frequent genetic variants as risk or protective alleles to common (polygenic) forms of liver disease. Illustrative examples are mentioned. NGS technologies can be used to identify variants across the allele frequency spectrum, while conventional GWAS using genotype arrays only identify common variants associated with disease. However, GWAS are increasingly using WES and WGS data, allowing the identification of both rare and common genetic variants that confer risk for or protection from disease. Abbreviations: GWAS, genome-wide association study; MASLD, metabolic dysfunction–associated steatotic liver disease; NGS, next-generation sequencing; PSVD, porto-sinusoidal vascular disease; SLD, steatotic liver disease; WES, whole-exome sequencing; WGS, whole-genome sequencing.

for liver disease.[27] Moreover, these studies have also uncovered genetic variants in *HSD17B13* and *CIDEB*, which provide protection against MASLD and liver disease in general.[27,28] Both *HSD17B13* and *CIDEB* encode proteins which associate with lipid droplets. Functional studies have demonstrated how loss of function of both of these proteins alters the dynamics of lipid droplet accumulation.[27,29] The characterization of these genes involved in hepatic lipid homeostasis allows for accurate stratification of each patient's risk of developing liver disease and for the development of novel therapeutic targets. Small-interfering RNAs targeting *PNPLA3* and *HSD17B13* are 2 illustrative examples of genetic medicine approaches currently being evaluated in clinical trials.[30]

The association of several genetic variants with MASLD has also encouraged the development of polygenic risk scores.[31–33] These represent a weighted sum of well-characterized disease risk alleles carried by an individual, in hopes of using them to better stratify individual disease risk and therefore more accurately inform disease management. While polygenic risk scores have been proposed to outperform any individual risk allele in predicting the risk of MASLD progression, robust data on their performance in the clinical setting are largely lacking. In addition, their efficacy in predicting long-term outcomes has yet to be evaluated.[33,34] In an attempt to incorporate genetic information into the stratification of HCC risk, variants impacting hepatic lipid accumulation and the Wnt/β-catenin pathway have recently been proposed to slightly enhance the performance of conventional clinical scores.[33] Additional studies with larger and more ethnically diverse cohorts are required to fully understand the interplay between risk and protective alleles, alongside environmental risk factors, to inform accurate disease risk stratification and appropriate management.

"Take-to-clinic message [1]": While polygenic risk scores for the management of MASLD are still not prime time for routine clinical practice, individuals who are overweight (BMI > 25), obese (BMI > 30), or morbidly obese (BMI > 35) and carry homozygous risk allele p.I148M in PNPLA3 have a considerably higher risk to progress to cirrhosis and develop HCC. Thus, clinicians may consider determining their patients' PNPLA3 p.I148M genotype to inform personalized counseling on lifestyle modifications and weight loss more effectively, particularly in individuals at higher risk of CLD progression and complications (Table 1, Figure 2).[35–37]

A genomic approach applied to autoimmune liver diseases, namely autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), has revealed insights into their underlying genetic determinants.[38] AIH is thought to be caused by loss of tolerance to liver antigens, while PBC and PSC represent the most relevant immune-mediated biliary diseases.[39–41] Similarly to other autoimmune conditions, these diseases are thought to exhibit complex

TABLE 1 Summary of 6 considerations for translating recent genomics-based knowledge in liver disease to clinical practice.

Clinical presentation	Genomics-based knowledge	Management considerations
"Take-to-clinic" messages		
[1] MASLD	• Individuals who are overweight, obese, or morbidly obese and harbor homozygous p.I148M in PNPLA3 have a higher risk of progression to cirrhosis and develop HCC	• Consider obtaining PNPLA3 p.I148M genotype to inform personalized counseling about lifestyle modifications/weight loss
[2] Unexplained liver disease	• Up to 30% of adults with liver disease of unclear etiology despite a comprehensive workup harbor a monogenic liver disease	• Consider genomic analysis in patients with idiopathic liver disease despite a comprehensive workup
[3] Hepatic steatosis in lean individuals	• Lean individuals with hepatic steatosis, transaminase elevation, and no alcohol overuse or visceral adiposity are more likely to have an underlying monogenic liver disease	• Consider genomic analysis in patients who meet these criteria
[4] Idiopathic cholestasis	• Nearly half of adults with idiopathic cholestasis appear to have an underlying monogenic liver disease	• Consider genomic analysis (WES or TGS panel) in adults with idiopathic cholestasis
[5] PSVD	• Novel genetic causes of PSVD are being discovered in children and adults	• Consider genomic analysis in patients with PSVD of unknown cause
[6] HCA	• HCAs with *CTNNB1* exon 3-mutations show a higher risk for malignant transformation	• Consider tumor molecular profiling (when a biopsy is performed) for optimal patient management

Abbreviations: HCA, hepatocellular adenoma; MASLD, metabolic dysfunction–associated steatotic liver disease; PSVD, porto-sinusoidal vascular disease; TGS, targeted gene sequencing; WES, whole-exome sequencing.

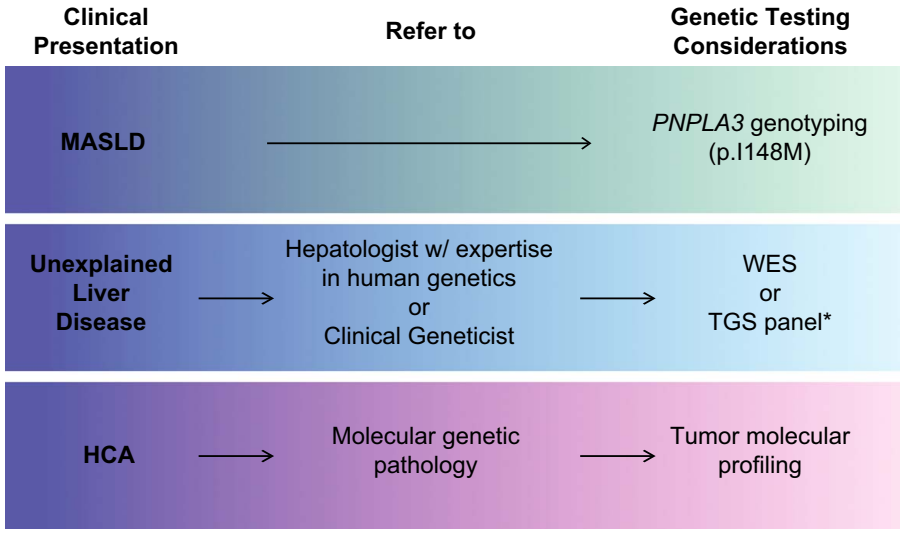

FIGURE 2 Framework for considering and incorporating genetic testing into the evaluation and management of patients with liver disease. Hepatologists may consider obtaining the *PNPLA3* p.I148M genotype for individuals with MASLD to assess their risk for progression to advanced liver disease. In cases of unexplained liver disease despite a thorough workup, genomic analysis is recommended as the next step, and referral to a hepatologist with expertise in human genetics or a clinical geneticist may be beneficial. *If there is strong suspicion for a specific group of genetic liver diseases (eg, cholestasis, iron overload, cystic liver/kidney disease, etc.), TGS for a relevant gene panel may be considered. Otherwise, unbiased WES should be considered. For patients diagnosed with HCA, referral to molecular genetic pathology for liver tumor molecular profiling is advised to guide further management. Abbreviations: HCA, hepatocellular adenoma; MASLD, metabolic dysfunction–associated steatotic liver disease; TGS, targeted gene sequencing; WES, whole-exome sequencing.

gene-gene and gene-environment interactions. A Danish study has estimated the pairwise concordance rate of AIH between monozygotic twins to be about 8.7%, suggesting relatively low heritability.[42] On the other hand, studies in monozygotic twins have found the pairwise concordance rate of PBC to be among the highest across all autoimmune diseases at 63%.[43] First-degree relatives of patients with PSC have also been found to harbor an increased risk of PSC.[44] In line with these findings, genome-wide association studies have identified susceptibility loci associated with these conditions, many of which are pleiotropic across other autoimmune diseases.[45] These include stronger associations with human leukocyte antigen (class I and II HLA genes) as compared with non-HLA loci.[45–50] These findings help to advance our understanding of these diseases, particularly those that diverge from the typical demographic profile for autoimmune diseases. This is the case for PSC, given its male predominance, as well as its relative lack of responsiveness to immunosuppression.[47] Moreover, large studies in certain ethnic groups, such as PSC in non-European individuals, are needed.[45] More detailed discussion of non-HLA susceptibility loci in AIH, PBC, and PSC can be found elsewhere.[51–53]

THE EVOLVING UNDERSTANDING OF MONOGENIC LIVER DISEASES

Despite the early characterization of various monogenic liver diseases, our understanding continues to evolve. The implication of the *HFE* gene in the pathogenesis of hereditary hemochromatosis (HH) paved the way for understanding the physiology of iron metabolism, leading to the discovery of other genes associated with HH, such as *HJV*, *TFR2*, and *HAMP*, and *SLC40A1*.[54–59] It has been reported that iron overload–related disease in individuals with p.C282Y homozygosity is more common in males than females, attributed largely to the physiologic loss of excess iron due to menstrual bleeding.[60] Our knowledge about the contribution of the p.C282Y and p.H63D *HFE* genotypes to disease burden has also continued to expand. While these genetic variants were initially described as causal for HH, large-scale genome sequencing studies have revealed that the frequency of these variants in the population is higher than expected, suggesting they more likely act as risk alleles contributing to the development of HH.[61,62]

Wilson disease is caused by biallelic variants affecting the gene *ATP7B*, encoding transmembrane copper-transporting ATPase 2. *ATP7B* is crucial for both facilitating the transport of copper into bile and its incorporation into the copper transport protein ceruloplasmin.[63] As copper is metabolized by the liver, the disease results in the accumulation of copper in hepatocytes and an excess of free serum copper in the bloodstream, presumably leading to pathologic accumulation in other tissues such as the brain.[63] Though a wide spectrum of genetic variants have been associated with the disease, attempts toward establishing genotype-phenotype correlations have been largely elusive.[63] Prevalence of the disease had previously been estimated to be 1/30,000 individuals, but a

study based on genetic case confirmation estimated this number to be higher at 1/7000.[64] Previous underestimates may result from a lack of consideration of this disease in differential diagnosis, as well as limitations in the adequate interpretation of *ATP7B* variants. One such example is the rare synonymous variant p.Phe764Phe (c.2292C > T, rs372979339) in *ATP7B*, which has been shown to cause skipping of exon 8, thought to result in functionally inactive protein.[65–67] Moreover, genetic testing should be performed to confirm the diagnosis of Wilson disease, as there are other rare genetic diseases that can mimic the clinical presentation of Wilson disease, such as MPV17-hepatocerebral mitochondrial DNA depletion syndrome 6, also known as Navajo neurohepatopathy.[68]

Alpha-1-antitrypsin (AAT) deficiency is a monogenic disease affecting the liver and lungs. Most individuals carry 2 copies of the normal PiM allele of the gene *SERPINA1* encoding AAT, which is synthesized by the liver and secreted into the bloodstream in homeostasis. In AAT deficiency, commonly the result of a homozygous p.Glu342Lys substitution (PiZ allele), an altered protein is produced and abnormally accumulates as AAT aggregates in hepatocytes, leading to liver toxicity. Subsequently, this results in AAT deficiency in circulation, and is therefore unable to perform its primary role in protecting the lung tissue from destruction by neutrophil elastase.[69] While the PiZZ genotype accounts for the majority of cases with severe disease, a milder form of the disease is seen in individuals who harbor p.Glu264Val (PiS allele).[69] The highest prevalence of the PiZZ genotype is detected in individuals of European descent, with 1/2000 Europeans affected with the disease; 1/25 individuals of European descent have the PiMZ genotype and appear to be at risk for milder liver disease.[69] This risk is compounded by the presence of coexisting conditions such as MASLD or alcohol use.[69–71] Liver disease manifestations of AAT deficiency can be highly variable in their presentation in both children and adults.[72–74] This disorder remains underdiagnosed, highlighting the importance of screening those for which there is high clinical suspicion of the disease.[69,75] The gold standard test is either AAT protein phenotyping or genotyping performed by an experienced reference lab.[73] While no therapies are currently available for the disease, a promising phase 2 trial using an RNA interference approach demonstrated efficacy in significantly reducing both liver AAT accumulation and liver enzyme measurements in those with the PiZZ genotype.[76]

Cystic fibrosis (CF) is caused by biallelic variants in the gene *CFTR*, encoding a chloride channel on the apical membrane of epithelial cells, leading to disease manifestations in the lungs, pancreas, gastrointestinal, and hepatobiliary tracts. *CFTR* is expressed throughout the biliary tract, and CF-related liver disease is thought to be caused by impaired bile flow, leading to retention of toxic bile acids and peribiliary fibrosis.[77] The F508del allele is the most common variant associated with the disease worldwide.[77,78] The characterization of CF-causing variants into 6 variant classes and their association with genotype-phenotype correlations at the population level have been well described elsewhere.[78,79] While numerous patients with CF have evidence of hepatobiliary disease, this is not clinically significant for most patients.[77] Progression to cirrhosis with portal hypertension is only seen in a minority of individuals with CF.[80] Disease manifestations in other organs, implications of genetic heterogeneity on management, and advancements in novel treatments have been comprehensively reviewed by others.[77,79]

RARE GENETIC VARIANTS UNDERLYING LIVER DISEASE PATHOGENESIS

While CLD can result from a variety of etiologies, up to 30% of the patients with cirrhosis and more than 10% of those under consideration for liver transplant have advanced liver disease of an unknown cause.[81] Implementing genomic analysis in cases of undiagnosed liver disease has been fruitful in the discovery of novel genetic liver diseases[82–89] expediting the diagnosis of pediatric liver diseases, and in some instances, limiting invasive liver biopsies. Furthermore, genomic analysis provides an actionable diagnosis for up to 30% of adults with unexplained liver disease despite a comprehensive workup.[4,5] This enables a definitive diagnosis, and therefore targeted treatment and management, while also facilitating the characterization of a broader phenotypic disease spectrum, which may not have been recognized in the absence of a molecular understanding of the disease pathogenesis.[4,5,90] These advances are largely due to the application of next-generation sequencing (NGS), which has transformed our ability to rapidly and effectively establish a link between rare genomic variation and disease (Figure 1). WES allows for the putative detection of any genetic variant within protein-coding regions, as well as adjacent intronic splice-site regions for nearly all the 20,000 human protein-coding genes. Given that about 85% of disease-causing variants are predicted to be in coding regions, which only represent ~1% of the entire genome, WES provides a balance between sequencing and storage cost, time of analysis, and scope of interpretable genetic information.[91] On the other hand, whole-genome sequencing, another application of NGS, which examines nucleotides across the entire (coding and noncoding) genome, provides a much larger amount of genetic information. However, it presents with increased costs and larger challenges in interpreting sequencing data as compared with WES. Thus, our incomplete understanding of linking genetic variation in noncoding regions of the human genome with disease has largely hindered the adoption of whole-genome sequencing in most clinical settings.[92–95]

Distinct from previously outlined diseases with well-characterized pathophysiology, the study of patients who do not fit the typical diagnostic framework is expanding the spectrum of liver-related Mendelian diseases.[96] An illustrative example is atypical presentations of common diseases such as steatotic liver disease (SLD).[97] SLD in lean patients (BMI <25) is estimated to occur in about 10%–20% of the population.[98,99] Patients with associated visceral adiposity and insulin resistance make up the majority of these cases and are thought to have similar drivers of disease as nonlean patients with MASLD.[3] However, lean patients with SLD without visceral adiposity or alcohol overuse appear to be more enriched with monogenic disorders as the primary drivers of disease.[3] Our group has previously identified several cases of SLD with monogenic causes among individuals with biopsy-proven SLD. This includes cases of familial lipodystrophy type 3 caused by *PPARG* deficiency, familial hypobetalipoproteinemia caused by *APOB* deficiency, and hereditary fructose intolerance caused by *ALDOB* deficiency, among others.[3,5,90] These genetic diagnoses allowed for targeted treatment in certain situations. This also highlights cases in which clinicians should consider a genetic diagnosis, particularly in the presence of an atypical phenotype or multisystemic involvement.[5,100,101]

"Take-to-clinic message [2]": Genomic analysis should be considered in adults with unexplained liver disease despite a comprehensive workup, especially if they also have any of the following features: 40 years of age or younger, multisystemic disease, congenital malformations, positive family history, or being offspring of a consanguineous union (Table 1, Figure 2).[100,102] This approach has been successful in uncovering a variety of known genetic liver diseases, some of them primarily described in pediatric patients and not traditionally included in the differential diagnosis in adults.

"Take-to-clinic message [3]": Genomic analysis should be considered in adults who are lean, with no visceral adiposity or alcohol overuse, and present with unexplained hepatic steatosis and transaminase elevation (Table 1, Figure 2).

Progressive familial intrahepatic cholestasis (PFIC) types 1, 2, and 3, which consist of monogenic disorders characterized initially in pediatric patients and attributed to rare biallelic variants in genes *ATP8B1*, *ABCB11*, and *ABCB4*, respectively, have played an integral role in our understanding of the genetic underpinnings of hepatobiliary pathology. These 3 genes encode proteins that are crucial for the appropriate composition of phospholipids and bile acids in bile. Alterations in these proteins are associated with varying disease onset and severity of cholestatic liver disease. *ABCB4*, which encodes for MDR3 protein, has been implicated in heterogeneous cholestatic diseases of varying severity, including PFIC3, intrahepatic cholestasis of pregnancy, and low phospholipid–associated cholestasis.[4,5,103,104] However, disease presentation can blur the lines of these conditions, subverting conventional thought on disease inheritance. While less severe disease such as intrahepatic cholestasis of pregnancy or low phospholipid–associated cholestasis is classically thought to result from rare heterozygous loss-of-function variants in *ABCB4*, PFIC3, which can progress to end-stage liver disease, requires recessive inheritance.[105] However, a number of studies have highlighted cases of patients with cryptogenic cirrhosis found to have only a single damaging allele.[106,107] While genetic modifiers and environmental interactions could be contributors to this clinical variation, additional studies are required to gain a clearer understanding of genetic and environmental contributors in these cases. Furthermore, novel monogenic causes of low and high gamma-glutamyl transferase cholestasis continue to be described, the scope of which has been outlined in a recent comprehensive review.[108]

Heterogeneity in cholestatic syndromes also extends to Alagille syndrome (ALGS), an autosomal dominant condition caused primarily by rare heterozygous loss-of-function variants in *JAG1*, or in a smaller proportion of patients due to rare heterozygous variants in *NOTCH2*. ALGS has long been known to show clinical variability, as patients within the same family often have varying clinical phenotypes.[109] Many patients receive a diagnosis purely based on the presence of classic diagnostic criteria.[109] However, genetic studies continue to reveal disease-causing *JAG1* variants in adult patients who many times do not meet the classic ALGS criteria, but rather, present with atypical disease, which would have been overlooked without a molecular diagnosis. This includes patients with predominantly renal and vascular involvement.[4,110–112] It has also been proposed the role of genetic modifiers contributing to the clinical heterogeneity in this syndrome.[113] Overall, these findings suggest that ALGS is likely underdiagnosed in adults, highlighting the need for increased awareness in the clinical setting.[4,112,114]

"Take-to-clinic message [4]": Nearly half of the adults with idiopathic cholestasis despite a comprehensive workup who underwent genomic analysis were found to have an underlying genetic cause for their disease, including patients diagnosed with ALGS and MDR3 deficiency in adulthood.[4,5] Thus, genomic analysis should be considered in the evaluation of these patients (Table 1, Figure 2).

Insights into porto-sinusoidal vascular diseases (PSVDs), a clinically heterogeneous group of disorders that coalesce into a common phenotype of noncirrhotic

portal hypertension, have been further elucidated by the recent discovery of several monogenic diseases underlying their pathogenesis.[115] These include rare biallelic variants in *DGUOK*, *GIMAP5*, and *TRMT5*, as well as heterozygous variants in *KCNN3*, *FOPV (C4ORF54)*, and *FCHSD1*.[82,83,116–119] *GIMAP5*, *KCNN3*, and *FOPV* have been suggested to contribute to maintaining the integrity of the liver vasculature, while *DGUOK* and *TRMT5* play a role in mitochondrial DNA maintenance. While these discoveries continue to enhance our understanding of PSVD, further research is required to disentangle the mechanisms among these heterogeneous disorders, for which we expect to illuminate innovative therapeutics.

"Take-to-clinic message [5]": Genetic causes should be investigated in individuals with features of porto-sinusoidal vascular disease of unknown cause (Table 1, Figure 2).

SOMATIC VARIANTS IN HEALTHY AND CIRRHOTIC LIVERS

The application of NGS to germline and tissue DNA from the same individual has also allowed the effective identification of somatic variants in non-oncological liver diseases. Recent studies have highlighted age-related increases in somatic variation in non-diseased liver, confirming previously observed findings. Despite the heterogeneity in variant burden detected in healthy individuals, cirrhotic livers were shown to have a significantly increased burden of somatic variants.[120–122] Furthermore, while a moderate number of genetic variants were found in healthy livers, structural variants, including chromothripsis, were much more common in cirrhotic compared to healthy livers. In patients with MASLD, an excess of somatic variants was observed in genes that protect hepatocytes from lipotoxicity.[120] These genes include *FOXO1*, a key insulin-signaling transcription factor, *CIDEB*, highlighted previously as implicated in germline protection from MASLD, and *GPAM*, which is thought to be a regulator of lipid processing and protecting hepatocytes from lipotoxicity.[27,123–125] Interestingly, none of *FOXO1*, *CIDEB*, and *GPAM* were found in excess in tissue samples from HCC.[120] The implication of genes in germline and somatic protection raises unique opportunities for exploring innovative therapeutic targets.

These findings raise further questions regarding the role of somatic variants in liver disease physiology. In addressing this question, one study used WES to profile nonmalignant diseased liver tissue and replicated previous findings of high mutational burden in tissue samples with severe disease.[126] Interestingly, further investigation in these samples with ultradeep sequencing of a target set of HCC-associated genes revealed recurrent variants in *PKD1*, *PPARGC1B*, *KMT2D*, and *ARID1A*, which were not found using standard coverage WES.[126] Subsequent murine validation revealed that loss of *Pkd1*, *Kmt2d*, and *Arid1a* was sufficient to promote clonal expansion and increase hepatocyte fitness.[126] In a separate study, this group leveraged a novel mouse platform for lineage tracing of somatic clones to identify genes that confer protection from steatosis, including *Tbx3*, *Bcl6*, and *Smyd2*.[127] While these studies have begun to uncover the contribution of somatic variants to liver disease pathophysiology, future studies will elucidate the scope of their contribution to progression and protection from CLD.

SOMATIC VARIANTS UNDERLYING MOLECULAR SUBTYPES OF HEPATOCELLULAR ADENOMAS

Hepatocellular adenomas (HCA) are rare benign liver tumors classically associated with excessive hormonal exposure, such as the use of oral contraceptives or anabolic steroids, as well as other conditions such as glycogen storage diseases and metabolic syndrome. Advances in NGS have facilitated the classification of HCA subtypes based on underlying genetic architecture, namely (i) *HNF1A*-inactivating HCA, (ii) *CTNNB1*-activating HCA, (iii) inflammatory HCA resulting from genetic alterations in *IL6/JAK/STAT* signaling pathway, and (iv) Sonic Hedgehog HCA, along with an unclassified group encompassing the remaining cases.[128]

HCAs with biallelic loss of *HNF1A* typically show marked steatosis with minimal cytological abnormalities or inflammatory infiltrates.[129,130] While most of these cases are found to be due to somatic biallelic inactivating variants, studies have noted up to 10% of cases demonstrating one inactivating allele of germline origin. As germline *HNF1A* variants are known to cause maturity-onset diabetes of the young type 3, it is important to consider the risk for the development of HCA in these patients.[131–133] HCAs due to alterations in *CTNNB1* typically lead to overactivation of the Wnt/β-catenin pathway. Subtypes of *CTNNB1*-activating HCA have also been identified, namely those with activating mutations in exon 3, or in exons 7/8. These subtypes are primarily distinguished by their different risk for malignant potential. HCAs with *CTNNB1* exon 3 mutation(s) demonstrate higher potential for malignant transformation as compared with HCAs with *CTNNB1* mutation(s) in exons 7/8 or other HCA subtypes. Thus, HCAs with mutation(s) in exon 3 are more likely to warrant surgical management.[128] Inflammatory HCA is characterized by variants in a variety of genes, including *IL6ST*, *FRK*, *STAT3*, *GNAS*, and *JAK1*, comprising up to 50% of cases and showing a strong association with

estrogen exposure. These genes are involved in the *IL6/JAK/STAT* pathway, leading to its activation and an inflammatory infiltrate within tumors.[134,135] Sonic Hedgehog HCA accounts for about 4%–5% of cases, resulting from somatic fusion events between the genes *INHBE* and *GLI1*. *GLI1* encodes a transcription factor in the Hedgehog pathway, and *INHBE* acts as the driver of *GLI1* activity in these HCAs.[128] Studies have also highlighted the association between this type of HCA and estrogen exposure, obesity, and an increased risk of bleeding complications.[136] These findings underscore the clinical importance of identifying these genetic subtypes, particularly in informing diagnostic and management strategies.

"Take-to-clinic message [6]":In cases where a biopsy of hepatocellular adenoma is obtained, tissue molecular profiling as described above should be considered. Genetic information will assist in disease subtype classification, determination of association with estrogen exposure, and assessment of risk for malignant transformation, with a direct impact on optimal patient care (Table 1, Figure 2).

SOMATIC VARIANTS UNDERLYING HCC

HCC is the most common type of primary liver cancer in adulthood, with its development often arising in background livers with chronic hepatitis B or cirrhosis.[137,138] Similarly to CLD, the global burden of HCC remains a public health challenge with a projection of over 1 million cases annually by 2025, largely driven by the obesity epidemic and MASLD.[139] Over the past decade, numerous studies have utilized NGS to investigate the genetic architecture of HCC. These studies have demonstrated that HCC is a highly heterogeneous malignancy with an average of 40–60 coding variants per tumor, including 2–6 of which are located in putative driver genes.[122] Mutations in the *TERT* promoter are the most common driver, detected in early low-grade dysplastic nodules, and increasing in prevalence as the dysplastic nodules progress to HCC.[122] Recurrent somatic mutations have also been identified in *CTNNB1*, *TP53*, *ARID1A*, *ARID2*, *RB1*, *AXIN1*, and *NFE2L2*, demonstrating the role of the Wnt/β-catenin pathway, cell cycle regulators, and chromatin remodelers in driving the progression to HCC.[140]

The heterogeneity of genetic variants observed in liver tumors introduces unique challenges in therapeutic development in HCC, limiting a treatment approach toward a single specific target. In addition, while both in vivo mouse and in vitro cell culture models can provide important insights into disease mechanism(s), both have limitations in their ability to model the complex biology contributing to the onset and development of human HCC. Despite these challenges, which also exist across other cancer types, an increasing number of studies in various cancers have demonstrated that genomic analysis of tumors can improve patient outcomes.[68,141–143] Thus, while the translation of HCC genomics into clinical decision-making in hepatology is lagging, continued efforts toward its future incorporation into patient care are needed.

A VISION FOR A (NEAR) FUTURE OF GENOMICS-INFORMED HEPATOLOGY CLINICAL PRACTICE

The wide range of recent discoveries highlighting the contribution of germline genetic variants to liver disease underscores the importance of continued investigation in this realm. Whether related to common or rare diseases, these findings offer valuable insights into our understanding of disease pathogenesis, with some of these observations being ready for translation to the clinic (Table 1).[102] Continued innovations, such as the release of the first human pangenome reference, are likely to enhance our understanding of ancestry-specific genetic factors and their impact on disease.[144] Furthermore, studies incorporating large population databases, such as the UK Biobank and the more diverse US-based *All of Us* cohort, will continue to facilitate advances in precision medicine.[145,146]

As NGS becomes an affordable tool in the research and clinical armamentarium, we anticipate that it will enable further discoveries across the spectrum of liver diseases. Beyond improving diagnosis and our understanding of disease pathogenesis, the next step is translating these findings toward optimal patient management and new effective therapeutic interventions.[27] Advances in understanding the diverse liver cell types and their respective gene expression profiles at the single cell level, in addition to breakthroughs in modeling the liver's microenvironment using humanized liver cell types within a mouse model and development of liver organoid model systems, allow for unprecedented approaches for the study of human liver physiology.[147–151] These approaches can be applied toward modeling patient's disease, therapeutic screening, and propelling the field of regenerative medicine.[152–154]

In the clinic, a key step in translating these findings into improvements in patient care is adopting a multidisciplinary, team-based approach. In many cases, discussion and collaboration with other specialists about what genetic test to order and how to properly interpret its results is recommended (Figure 2). Numerous institutions host dedicated sessions for the discussion of oncology cases known as "tumor boards," drawing additional insights from imaging, pathology, and genetics to optimize patient care. We envision the development of

similar forums for the discussion of genetic disease cases with significant liver involvement, many of which benefit from the participation of members across different fields to provide expertise in achieving a proper diagnosis and to guide appropriate management. Accordingly, some institutions have already begun to establish these forums (eg, Hepatology Genome Rounds).[102] This provides a crucial step forward in accelerating the translation of new knowledge generated through research endeavors toward our goals of precision medicine and excellent patient care in hepatology.

AUTHOR CONTRIBUTIONS

All authors conceptualized, wrote, reviewed, and approved the final manuscript.

FUNDING INFORMATION

Silvia Vilarinho is supported by the NIH/NIDDK (R01 DK131033) and Doris Duke Charitable Foundation Grant #2019081. Shanin Chowdhury is supported by the National Institute of General Medical Sciences of the National Institutes of Health under award 1T32GM136651-01. 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

Silvia Vilarinho served as a consultant to Albireo Pharma, Inc., and receives research grant support from Moderna Therapeutics, Inc. The remaining authors have no conflicts to report.

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How to cite this article: Konkwo C, Chowdhury S, Vilarinho S. Genetics of liver disease in adults. Hepatol Commun. 2024;8:e0408. https://doi.org/10.1097/HC9.0000000000000408