Published in final edited form as:

Semin Liver Dis. 2015 November ; 35(4): 432–433. doi:10.1055/s-0035-1568133.

Commentary on Diagnostic Problems in Hepatology Cases

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Case1

In their article, “Beneath The Copper—Pediatric Wilson's Disease Cirrhosis and Hepatocellular Carcinoma: A Case Report,” Rosencrantz et al report the youngest case of Wilson's disease with hepatocellular carcinoma (HCC) to date. Such early-onset severe disease suggests genetic contribution to this outcome. Appropriately, the authors review the molecular genetics of Wilson's disease. The authors discuss how most individuals affected with Wilson's disease are compound heterozygotes, meaning that they have two different mutations affecting the same gene, *ATP7B*, which cause the disease. The authors highlight that more than 780 mutations in *ATP7B* are reported worldwide in the Human Genome Mutation Database, of which 508 are believed to be disease causing. They discuss how individuals of European, East Asian, and Indian ancestry most commonly harbor the H1069Q (exon 14), R778L, and C271X mutations in *ATP7B*, respectively. They further note that mutations in other geographic and ethnic groups vary considerably, are uncommon, and are virtually unique to these groups. Because only common known mutations in *ATP7B* can be assayed, the diagnosis of Wilson's disease is often missed as most individuals with Wilson's disease are not homozygous for these mutations. With exome sequencing becoming more available and affordable, detecting changes in the coding regions of genes, including compound heterozygous mutations in *ATP7B*, to diagnose Wilson's disease will become routine. If this testing is done early enough (possibly at birth), diseases such as Wilson's could be diagnosed before the onset of symptoms and copper chelation instituted to delay or prevent the disease. Furthermore, these same tools can identify genetic changes in tumor versus normal tissue that promote tumor development which can be immediately targeted to facilitate personalized treatment of cancer (see Case 4).

Case 2

In “Hepatic Fibrinogen Storage Disease in a Patient with Hypofibrinogenemia: Report of a Case with a Missense Mutation of the *FGA* Gene,” Lee et al describe a case of a 9-year-old boy who was found to have elevated liver function tests that ultimately led to a diagnosis of hypofibrinogenemia with liver fibrinogen storage disease. This case shows how easy it can

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Issue Theme Genome-Wide Association Studies and Liver Disease; Guest Editor, Elizabeth K. Speliotes, MD, PhD, MPH

be to make a clinical diagnosis using whole exome sequencing. Fibrinogen is a heterodimer composed of two sets of alpha, beta and gamma chains. A mutation in any one of the chains can cause problems for the molecule overall. Three types of defects in fibrinogen are known: afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia. Cases of afibrinogenemia and hypofibrinogenemia usually result from severe (i.e., deletion, frameshift, nonsense or splicing mutations) homozygous or compound heterozygous mutations of any of the fibrinogen genes. Three genes code for fibrinogen chains: alpha (*FGA*), beta (*FGB*), and gamma (*FGG*). Most cases of dysfibrinogenemia occur in patients heterozygous for missense mutations in *FGA*. These mutations presumably create a full-length fibrinogen molecule that heterodimerizes but causes abnormal fibrin polymerization and interferes with the function of the polymer. In all three types, sequestration of fibrinogen in hepatocytes is not a prominent feature. Most patients with qualitative or quantitative defects in fibrinogen come to clinical attention because of bleeding problems. More recently, however, a fourth pattern of defects has been noted. These patients, who are heterozygous for missense mutations in *FGG*, have liver damage with elevations in their liver enzymes in addition to bleeding problems. When characterized, they have hypofibrinogenemia and hepatic endoplasmic reticulum storage disease as the cause of their disease. The case here is novel because the proband is heterozygous for a missense mutation in *FGA*, not in *FGG*, which also causes hypofibrinogenemia and hepatic endoplasmic reticulum storage disease. Using whole exome sequencing, the authors were not only able to check for the presence of the *FGG* mutation, previously reported to cause this constellation of symptoms, but they were also able to pinpoint a new mutation in *FGA* that also causes this constellation of phenotypes. Thus, exome sequencing, which is already standardized, affordable, and available for use, may soon become the test of choice for identifying not only known but also novel coding variants of clinical significance.

Case 3

In their study, “Hepatocellular Carcinoma Arising in an *HNF-1α*-Mutated Adenoma in a 23-Year-Old Woman with Maturity-Onset Diabetes of the Young: A Case Report,” Struck et al report the development of HCC within an *HNF-1α* hepatocellular adenoma. Because malignant transformation of a hepatic adenoma is exceedingly rare, it would have been interesting to show the molecular change in *HNF-1α*, as it may be a novel change in the protein with malignant potential. Furthermore, even though maturity-onset diabetes of the young (MODY) can be caused by mutations in *HNF-1α*, and mutations in *HNF-1α* are also one of the three most common molecular changes found in hepatic adenomas, the mutations that cause MODY are not usually the same as the somatic mutations that predispose to development of hepatic adenomas. Thus, molecular characterization of this *HNF-1α* allele would have been interesting. Evidence is mounting that HCCs can arise even in noncirrhotic livers, and in these cases the mechanism of how these tumors develop may differ from HCCs that arise in the setting of cirrhosis. The authors note that this HCC did not have mutations in exon 3 of *CTNNB1* and the *TERT* promoter, the most common mutations seen in HCCs to date. Some researchers have proposed that alterations in insulin signaling or diabetes may create a permissive environment in which HCCs can develop even in noncirrhotic livers (see comment on Case 4, below). In the present case, the patient also had MODY, which could

have facilitated development of HCC by creating a permissive metabolic environment for development of cancer. Analysis of normal liver, the adenoma, and the HCC using exome, if not whole-genome, sequencing could have identified possible genetic drivers of malignant transformation while also ruling out alternative causes for the hepatic adenoma (e.g., mutations in beta-catenin). Thus, exome sequencing may soon supplant Sanger sequencing, which is the current standard of care and was utilized to carry out the molecular analyses reported.

Case 4

In “Hepatocellular Carcinoma in Noncirrhotic Liver with Glycogenotic Foci: Basic Science Meets Genomic Medicine,” Lefkowitz et al describe a case of a man who developed HCC without having liver cirrhosis or other known risk factors for development of the disease, such as hepatitis or nonalcoholic fatty liver disease. Although most HCCs arise in the setting of liver cirrhosis, recent evidence suggests that about 25% of these occur in noncirrhotic livers. The molecular and genetic mechanism of how these noncirrhotic HCCs arise is only just now beginning to be elucidated. Here, the authors note that some liver cells near the tumor had glycogenotic foci. They discuss how cancer cells can promote their survival by channeling glucose toward the pentose phosphate pathway and glycolysis, in what is referred to as the “Warburg effect.” They suggest that such metabolic changes may have predisposed this individual, who has no other risk factors for HCC, to develop the disease. They note that there have been reports of abnormal insulin signaling or diabetes itself perhaps predisposing to HCC (see also Case 3), but the molecular mechanisms of how these metabolic effects predispose to cancer are not known. Toward understanding the molecular changes that predispose to cancer formation, these authors use next generation sequencing to identify amplification in four genes and a rearrangement at a fifth locus in the tumor. These changes have been reported to be present in other HCCs but are not the most common changes seen in HCCs and thus may identify an emerging subtype of HCC. They discuss how the amplified genes play roles in cell proliferation and survival and how they might promote tumor formation. Use of next generation sequencing like this can quickly and economically identify the genetic changes in any tumor compared to nearby normal tissue, to not only better define the molecular drivers of carcinogenesis but also to potentially target them for intervention. Because the changes noted in this tumor, for example, are not the same as ones typically seen in HCC (*TP53* and *CTNNB1* and *TERT* promoter), therapies based on targeting the known HCC pathways would not be effective for this person's tumor. In this way, then, knowledge of the molecular changes in a particular person's tumor allows for instant personalization of therapy. Is personalization of treatment feasible, tractable, and affordable? With recent technological advancement, including the ability to specifically target genes for deletion using cas9/CRISPR genome editing, for example, this could become a reality sooner than we think. Indeed, the hope is that by matching the treatment to the molecular needs of the patient, we may be able to provide better care at lower costs versus the care we provide presently in which nonspecific treatments for disease often do not work or have intolerable side effects.