



Your Liver. Your Life.

Northern California Chapter

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National HelpLine 1-800-GO-LIVER (1-800-465-4837)

American Liver Foundation Research Award: Genetic Dissection of Non-Alcoholic Steatohepatitis (NASH)

by Bradley E. Aouizerat, PhD

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver injury associated with liver cell fat accumulation in the absence of significant alcohol consumption. Nonalcoholic steatohepatitis (NASH) is a part of the NAFLD spectrum and is characterized by the presence of excess fat in the liver (steatosis) accompanied by variable liver cell inflammation and death and/or scarring (fibrosis). NASH is frequently associated with hyperlipidemia, obesity and insulin resistance, with insulin resistance as a common underlying metabolic abnormality, and can progress to cirrhosis and end-stage liver disease requiring transplantation. The accumulation of fat, as triglyceride in liver cells, is the first step in the development of NASH.

Often associated with obesity, NASH is becoming increasingly prevalent in the United States and is commonly recognized in children. A recent review estimated the population prevalence of NASH as high as 2-3%. The propensity of NASH to progress to more advanced liver disease is a primary concern. Studies suggest that between 16-30% of affected individuals will have a progressive course, resulting in fibrosis and cirrhosis and an increased risk of liver cancer. In view of the prevalence of NASH, even a low rate of progression to end-stage liver disease has enormous public health implications [see **Figure 1.**]

The underlying pathophysiology of NASH is poorly understood. Obesity, diabetes, elevated levels of fat in the blood (hyperlipidemia) and insulin resistance are common associations of NAFLD. However, the occurrence of NASH without these associations and the occurrence of diabetes, hyperlipidemia, obesity and insulin resistance without NASH strongly suggest other unidentified factors, likely genetic, that critically influence the risk of developing fatty liver disease and its subsequent progression to NASH and beyond. While insulin resistance is fundamental, the disease is likely multifactorial, involving both genetic and environmental factors that regulate lipid metabolism and the flux of fat as triglyceride to, within and from the hepatocyte. A current mechanistic model for NASH proposes the development of steatosis as a “first hit,” sensitizing the liver to subsequent oxidative stress/cytokine injury (the “second hit”) leading to progressive liver disease. This rational model is ideal for the nomination of candidate genes for NASH, particularly genes that regulate critical pathways of lipid metabolism and the flux of fatty acids and triglyceride to, within and from the liver.

Lipid disorders of genetic origin are already of major public health importance because of their impact on cardiovascular disease, and disorders of lipid homeostasis that result in the accumulation of fat underlie all forms of fatty liver disease. I have previously characterized several genes predisposing to familial combined hyperlipidemia, a disease leading to a 10- to 20-fold increased risk of premature heart attack. Several of these genes functioned to regulate the flow of fat to and from the liver. A series of collaborations with clinicians studying NAFLD at UCSF led to the formulation of a theory that a subset of genes contributing to combined hyperlipidemia could also lead to NASH – and a pilot study funded in part by the UCSF Liver Center confirmed this novel hypothesis. These findings serve as the basis for my research, funded by the AASLD/ALF Liver Scholar Award, to identify further genetic risk factors for NASH. Thus far, our team has identified variations in five genes that appear to be more common in individuals with NASH. It is my hope that by identifying these genetic determinants, we will not only better understand the mechanism(s) leading to NASH, but also identify less invasive methods of diagnosis and perhaps even a means of identifying those who may benefit most from emerging therapeutic interventions, thereby reducing the risk of disease progression to cirrhosis and the need for liver transplantation.



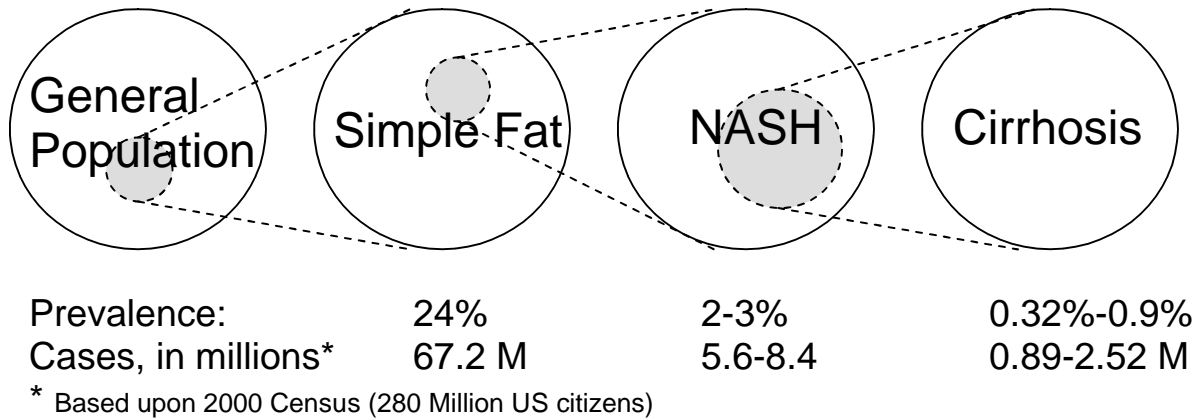
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Figure 1.



Dr. Aouizerat is an Assistant Professor in the Department of Physiological Nursing at the University of California, San Francisco. He received a \$150,000 Liver Scholar Award from the American Liver Foundation in 2004.