



**HELEN HOBBS, M.D.**

FATTY LIVER DISEASE:  
ANCIENT MUTATIONS FOR A COMMON DISEASE

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208 LIGHT HALL



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Upcoming Discovery Lecture:

SANDRO GALEA, M.D., M.P.H., Dr.P.H.

*Dean and Robert A. Knox Professor, School of Public Health, Boston University*

*January 24, 2019  
208 Light Hall / 4:00 P.M.*

VANDERBILT UNIVERSITY  
MEDICAL CENTER

## FATTY LIVER DISEASE: ANCIENT MUTATIONS FOR A COMMON DISEASE

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Fatty liver disease (FLD) is a burgeoning health problem affecting one-third of adults in the United States. The hallmark of FLD is the accumulation of triglyceride in cytoplasmic lipid droplets of hepatocytes (steatosis). In a subset of individuals, steatosis elicits an inflammatory response (steatohepatitis), which can progress to cirrhosis and hepatocellular carcinoma. Incomplete understanding of the pathogenesis of FLD has limited the development of therapies to arrest progression of the disorder. The Hobbs-Cohen lab has used exome-wide association studies to identify genes contributing to the development of FLD. These studies have revealed sequence variations in two genes - PNPLA3 (I148M) and TM6SF2 (E167K) - that are strongly associated with steatosis. Both variants are also associated with progression of FLD (both nonalcoholic and alcoholic). Recently, we identified a variant in HSD17B13 (A192Lfs8) that does not significantly affect liver fat content but confers protection against FLD progression. The mechanisms contributing to the pathogenesis of liver disease associated with the variants and the implications for disease prevention and treatment will be discussed.



### HELEN HOBBS, M.D.

1995 DALLAS HEART BALL CHAIR IN CARDIOLOGY RESEARCH

EUGENE McDERMOTT DISTINGUISHED CHAIR FOR  
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PHILIP O'BRYAN MONTGOMERY, JR., M.D.,  
DISTINGUISHED CHAIR IN DEVELOPMENTAL BIOLOGY

PROFESSOR OF INTERNAL MEDICINE AND  
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Dr. Helen H. Hobbs is a physician-scientist who attended Stanford University and Case Western Reserve Medical School before training in internal medicine at Columbia-Presbyterian Hospital in New York City and the University of Texas Southwestern Medical Center in Dallas, TX. After completing a post-doctoral fellowship in the laboratory of Drs. Joseph Goldstein and Michael Brown, she joined the faculty of UT Southwestern. Since 2002 she has been an Investigator of the Howard Hughes Medical Institute. In 1999, she established the Dallas Heart Study (DHS), a phenotypically well-characterized, multiethnic, population-based study. Together with Jonathan Cohen, in this population she showed that low frequency variants contribute to complex traits and diseases. They discovered that loss-of-function variants in PCSK9 lower plasma levels of LDL-cholesterol and confer protection from heart disease. These observations led to the rapid development of two FDA-approved, anti-PCSK9 antibodies for the treatment of hypercholesterolemia and the prevention of coronary atherosclerosis. In a similar fashion, they have identified mutations in selected members of the angiopoietin-like family (ANGPTL-3, -4, -8) that lower plasma lipid levels. More recently, they identified sequence variations that are associated with the full spectrum of alcoholic and nonalcoholic fatty liver disease (FLD), including steatosis, steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC).

Dr. Hobbs was elected to the Institute of Medicine in 2004 and the National Academy of Sciences in 2007. She was awarded the Breakthrough Prize in Life Sciences in 2015, the Passano Award (with Jonathan Cohen) in 2016, and the Harrington Prize for Innovation and Medicine (2018).

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