Host Genetic Variants in Obesity-Related Nonalcoholic Fatty Liver Disease

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KEYWORDS

• SNP • GWAS • Polymorphism • Steatosis

KEY POINTS

- Identifying genetic associations with nonalcoholic fatty liver disease (NAFLD) may offer insights into the mechanisms of disease pathogenesis, provide new diagnostic tools, and identify new therapeutic targets.
- Single-nucleotide polymorphisms (SNPs) or polymorphisms are single nucleotide substitutions in DNA that may result in the altered expression of a particular gene or altered function of the expressed protein.
- SNPs may be used in combination panels to better predict disease susceptibility and subsequent resolution.
- Future directions in genome-wide association studies need to include studies of SNPs from major regulatory genes in large cohorts of multiethnic populations to fully illustrate the combinatorial effects of these changes.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease over the last 3 decades.[1,2] NAFLD is a spectrum of disorders characterized by the deposition of fat in the liver, steatosis, which is not caused by significant alcohol consumption. Steatosis may progress to nonalcoholic steatohepatitis (NASH) in which there is inflammation, with a 20% risk of progressing to fibrosis and cirrhosis (**Fig. 1**).[3] Despite numerous lines of research on NAFLD, the epidemiology and natural history of NAFLD

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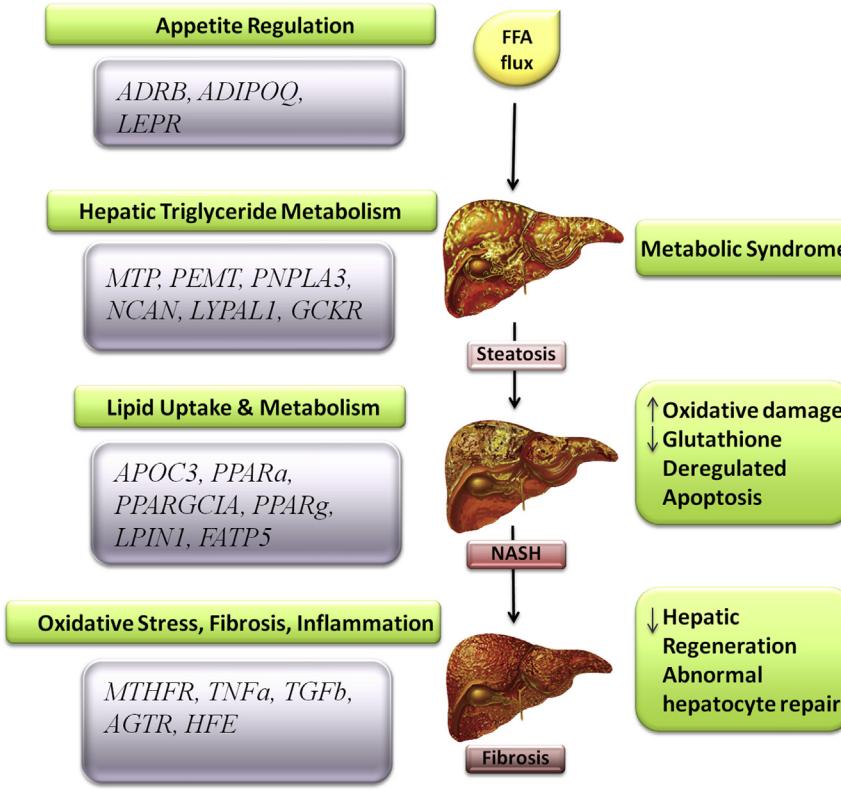

Fig. 1. Sequential steps of NAFLD pathology and the genes involved in pathways implicated in NAFLD. FFA, free fatty acids.

remain incompletely understood.[1] NAFLD is estimated to affect more than 35 million people in the United States and 28 million people worldwide.[4] Unfortunately, the prevalence of NAFLD in the general population is often underreported, largely because of a lack of symptoms in the early stages and, therefore, varies widely, ranging from 19% to 45%.[4] This variability may also be attributed to the inherent sensitivities of the different tools used in the diagnosis of NAFLD, such as liver enzymes (alanine transaminase [ALT]), ultrasound, magnetic resonance spectroscopy, biopsy, and so forth.[1] In Spain, a multicenter cross-sectional study shows the prevalence of NAFLD to be at 26% of the general population.[5] Another study reported a 42% prevalence of biopsy-proven NASH in Bangladesh, similar to reports from Western countries.[6] The overall prevalence of NAFLD in the participants of the Dallas Heart Study, a multiethnic population-based study in Dallas County, Texas, was 34% using magnetic resonance spectroscopy for hepatic triglyceride quantitation.[7] Although the prevalence of NAFLD based on elevated aminotransferases (ALT and aspartate transaminase [AST]) alone is between 7% and 11%, this is most likely an underestimation because numerous studies using biopsy as the diagnostic tool have shown that aminotransferases can be normal in individuals with NAFLD. As expected, liver biopsy of potential living donors for liver transplantation estimated the prevalence of steatosis as 20%.[8]

NAFLD is a complex disease with interplay between environmental and genetic factors contributing to the considerable variability of the natural history of the disease. A