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REVIEW

Genetics of Nonalcoholic Fatty Liver Disease: An Overview

Jharna Puppala [a], Siva Prasad Siddapuram [b], Jyothy Akka [a], Anjana Munshi [a,*]

[a] *Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Begumpet, Hyderabad 500016, India*
[b] *Asian Institute of Gastroenterology, Somajiguda, Hyderabad 500082, India*

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the world today. Its incidence in adults and children is rising rapidly due to the ongoing epidemics of obesity and type 2 diabetes. Hence, it has become a global public health issue. Environmental factors have been found to play a major role in the etiology of NAFLD, especially for genetically susceptible populations. Among these, one of the most important factors is junk food, especially the typical "Western-style" diet rich in simple carbohydrates, saturated fat, and highly processed food materials. Genetic predisposition to NAFLD does occur; however, a precise definition of genetic factors responsible for NAFLD is still lacking. Specific variants of different genes have been shown to present a risk for NAFLD. Genetic studies might be helpful in the management of the disease by developing novel treatment strategies based on individual's genotype.

KEYWORDS: Nonalcoholic fatty liver disease; Obesity; Type 2 diabetes; Genetic factors

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common liver disorder causing liver steatosis, which might in turn progress into steatohepatitis, fibrosis and even hepatocellular carcinoma. It is characterized by an increased fat content within the liver and elevated liver enzymes such as hepatic transaminases and alteration in the lipid profile. It may respond to treatments originally developed for insulin-resistant states such as type 2 diabetes (T2D). NAFLD has been commonly associated with obesity, T2D, dyslipidemia and insulin resistance (Adams and Angulo, 2006). All of these are the components of the metabolic syndrome, which strongly supports the notion that NAFLD is the hepatic manifestation of the metabolic syndrome. Nonalcoholic steatohepatitis (NASH) is the severe form of NAFLD and it leads to cirrhosis in 20% of the patients (Clark and Diehl, 2003). It may be considered a 'disease of affluence' and as a result is certainly on the rise in frequency (Das et al., 2006).

Across the globe, the frequency of NAFLD varies from 6.3% to 33% with a median of 20% based on a variety of assessment methods. While the occurrence of NASH ranges from 3% to 5%, the exact prevalence of NASH cirrhosis in general population has not been established yet (Chalasani et al., 2012). The incidence of NAFLD varies widely depending on the population studied and the definition used, which is 15%−40% in Western countries and 9%−40% in Asian countries (Amarapurkar et al., 2007). Data collected by National Health and Nutrition Examination Surveys from 1988 to 2008 revealed that the prevalence of other chronic liver diseases (CLDs) is stable whereas that of NAFLD is rising rapidly, due to the rise in metabolic conditions (Younossi et al., 2011).

Over the last several years, much progress has been made in terms of understanding its risk factors, pathogenesis, natural history, non-invasive markers and treatment strategies (Chalasani et al., 2012). Diet, exercise, and possible small bowel bacterial overgrowth are obvious environmental factors influencing the risk of NAFLD (Day, 2006; Mensink et al., 2007). Oxidative stress plays a key role in causing hepatocellular damage and progression of the disease in NASH

* Corresponding author. Tel/fax: +91 40 2340 3680.
E-mail address: anjanadurani@yahoo.co.in (A. Munshi).

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patients. Treatment of the patients with vitamin E as an antioxidant is effective in the management of NASH (Chalasani et al., 2012). It has been reported that a higher intake of saturated fat and a lower intake of the antioxidant vitamins C and E probably lead to NASH in obese patients but not in obese controls in the absence of liver disease (Musso et al., 2003). Studies involving families have detected significant evidence for heritability, indicating that the genetic determinants are important but the extent of predisposition is not known (Osterreicher and Brenner, 2007). In recent years, there have been several parallels of research to establish the functional variants of some candidate genes and the risk of NAFLD (Day, 2006).

FAMILY STUDIES OF NAFLD

The role of genetic factors in the pathogenesis of NAFLD has been suggested by two family studies. Struben et al. (2000) reported that NASH and cryptogenic cirrhosis exist together. This phenomenon was observed in seven out of eight children studied. Willner et al. (2001) found that 18% of patients with NASH had an affected first degree relative. All the relevant genetic information has almost come from classical case−control, candidate gene and allele association studies thus far because of difficulties in performing linkage studies in NAFLD. Therefore, many initial reports of positive associations are likely to be subject to chance findings (type I errors) while negative reports may be under powered studies which belong to type II errors (false negatives).

It has been strongly implicated from the previous studies that NAFLD is an inherited disease (Schwimmer et al., 2009). They studied 44 children with or without NAFLD and 152 family members of these children, and found that the rates of NAFLD were much higher in family members of children with NAFLD. This study suggests that family members of children diagnosed with NAFLD should get themselves screened even if they do not show symptoms. In most cases, the individuals suffering with the disease did not know about this. In a few cases, disease has already progressed to the severe level without the appearance of the symptoms. Understanding that this disease is hereditary, it will help an entire family to develop healthy habits with regular exercise and a healthy diet. Screening of family members of the affected individuals might be helpful for early detection at a stage where the disease is reversible and further complications may be prevented before the onset of cirrhosis. NAFLD is not only due to overweight and other associated conditions but also a genetic component.

INTERETHINIC VARIATIONS

Interethnic variations have been reported on the prevalence of NAFLD and NAFLD-related cryptogenic cirrhosis (CC) (Browning et al., 2004). Coexistence of NASH with other risk factors such as overweight and T2D can cause CC in most of the cases. The prevalence of obesity and T2D in U.S. has already been established whereas the prevalence of NASH or CC in different U.S. ethnic groups is not yet reported. A previous study (Browning et al., 2004) assessed the demographic characteristics of patients with CC at a U.S. county hospital based on a racially, ethnically diverse patient population. Forty-one patients (12 men, 29 women) were included in this study, and among these, 68% were obese (BMI $\geq$ 30) and/or had T2D and 74% of liver biopsies revealed one or more features of NASH. Of patients with CC, 68% were Hispanic while only 7% were African American. Despite a similar prevalence of type 2 diabetes among Hispanics and African Americans, the prevalence of CC was reported to be 3.1-fold higher and 3.9-fold lower, respectively, in comparison with European American patients. Findings of this study support the hypothesis that NASH associated with obesity and T2D, is responsible for developing CC in the majority of the cases in Hispanics and European Americans. Recent studies also support that this form of cirrhosis is unexpectedly rare among African Americans. A recent study has also shown that Hispanics are at greater risk for both NAFLD and NASH (Williams et al., 2011).

The effect of ethnicity on the clinicopathological profile of NAFLD patients has been studied due to ethnic differences in the occurrence of metabolic syndrome and its components (Misra and Misra, 2003). One such study showed that the prevalence of insulin resistance, defined as the lower quartile of insulin sensitivity index, was approximately 2−3 folds higher in Asian Indians than in other ethnic groups (Petersen et al., 2006). Further, Asian-Indian men had an approximately 2-fold higher hepatic triglyceride content and plasma interleukin-6 (IL-6) concentration than Caucasian men (Petersen et al., 2006). As per the Asian-Pacific criteria the majority of the Indian patients with NAFLD are overweight or obese even though they do not have morbid obesity as seen in Western patients (Duseja, 2006). In addition, the Indian patients also have a lower frequency of metabolic syndrome including its components such as T2D and hypertension, lower frequencies of hemochromatosis gene mutation and the presence of histologically milder disease at the time of diagnosis in comparison with the Western counterparts. However, data on the natural history of NAFLD as well as the rates of serious significant CLDs in Indian patients is lacking. Therefore, further prospective and cooperative studies are required (Amarapurkar et al., 2007).

GENETIC VARIANTS ASSOCIATED WITH NAFLD AND NASH

Pathophysiology of NAFLD has not yet been well understood. The so called ‘two hits’ model of the pathogenesis of NAFLD was proposed in 1998 (Day and James, 1998). According to this hypothesis, fat accumulation in the liver is the ‘first hit’. It is a consequence of excessive triglyceride accumulation caused by incongruity between influx and synthesis of hepatic lipids on one side and their β-oxidation and export on the other (Donnelly et al., 2005) (Fig. 1). A ‘second hit’ is necessary for the NAFLD disease to progress to NASH and cirrhosis. It is now established that hepatic lipid accumulation is not the sole factor responsible for