The Genetics of Pediatric Nonalcoholic Fatty Liver Disease

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KEYWORDS

• Nonalcoholic steatohepatitis • Children • Liver • Steatosis • *PNPLA3* • *TM6SF2* • Obesity • alanine aminotransferase

KEY POINTS

- Genetic polymorphisms play a role in the pathogenesis and severity of pediatric nonalcoholic fatty liver disease (NAFLD).
- The *PNPLA3* I148 M variant is associated with higher alanine aminotransferase in children with obesity.
- The *TM6SF2* (rs58542926 c.449 C > T, p.Glu167Lys) variant allele is associated with hepatic steatosis in children.
- Future studies of the genetics of pediatric NAFLD should focus on histologic severity and/or clinical outcomes.
- Replication studies will be important due to the heterogeneity in pediatric NAFLD by age, gender, race, and ethnicity.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children. The prevalence of fatty liver, after adjusting for age, race, gender, and ethnicity, is estimated at 9.6%.[1] Pediatric nonalcoholic steatohepatitis (NASH) can be distinct from adult NASH and denotes hepatic steatosis with inflammation, with or without ballooning injury to hepatocytes.[2] This can include zone 3 (venule)–centered injury pattern or confluent pattern typically with ballooning or portal predominant (zone 1)–centered injury pattern often without ballooning.[3] Children with zone 1 steatosis are more likely to present with fibrosis, including advanced fibrosis, compared with

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children with zone 3 steatosis.[4] Severe fibrosis and cirrhosis are observed in some children with NAFLD and can occur within a few years of diagnosis in the most severe cases.[5] Children with NASH are at higher risk of serious comorbidities, such as type 2 diabetes and hypertension.[6,7] Knowledge of the genetics of pediatric NAFLD may someday improve both diagnosis and treatment. NAFLD is now the leading cause of liver transplantation in young adults, yet a treatment remains to be discovered. Tailoring therapeutics to genetic predispositions is an avenue yet to be explored for this disease.

It is likely that NAFLD has a strong genetic component based on 2 key observations. First is the racial and ethnic difference in the prevalence of NAFLD and second is the evidence that NAFLD tends to cluster in families. Hispanic children have the highest prevalence of NAFLD and black children have the lowest. In the Study of Child and Adolescent Liver Epidemiology, in which diagnosis was based on liver histopathology, NAFLD was present in 11.8% of Hispanic children, 10.2% of Asian children, 8.6% of white children, and 1.5% of black children.[1] These differences have also been seen in adulthood.[8]

The clustering of NAFLD within families was evaluated by a heritability study by Schwimmer and colleagues.[9] In this study, 33 obese children with biopsy-proved NAFLD, 11 obese children without NAFLD, and 152 of their family members (parents, siblings, second-degree relatives, or third-degree relatives) were studied. Presence of NAFLD in family members was evaluated by MRI proton density fat fraction. In children without NAFLD, 17% of siblings and 37% of parents had NAFLD compared with 59% of siblings and 78% of parents of children with biopsy-proved NAFLD. The heritability estimates (with 0 no heritability and 1 representing a trait that is completely heritable) were 0.85 for the unadjusted dichotomous variable for NAFLD and 1.0 after adjusting for age, gender, race, and BMI. For the continuous measurement of hepatic steatosis, the adjusted heritability estimate was 0.39 or 39%.

Many aspects of the pathogenesis of NAFLD, such as the mechanism for the progression from steatosis to steatohepatitis, remain unclear. Additionally, it is not known why NAFLD occurs in some obese individuals and not others. Although less common, NAFLD also exists in 5% of children with a normal BMI.[1] With respect to treatment, there is wide variability in the response of children with NAFLD to lifestyle interventions,[10] and the underlying genetics of NAFLD may play a part in the differential response to dietary and/or exercise interventions. These observations suggest that genetics are a modifying factor and that there is an interplay of genetics and environment in the pathogenesis of this disease. Understanding how genes influence the development and progression of pediatric NAFLD will help to address critical gaps in knowledge in the field.

In this review, the existing data on the genetics of pediatric NAFLD are summarized. The articles cited were identified based on a search of PubMed done in February 2017 using the criteria “NAFLD and genetic and children” with the results limited to studies in humans.

PNPLA3

PNPLA3 belongs to the patatin-like phospholipase domain-containing family of proteins and it encodes a 481–amino acid protein called adiponutrin, which is involved in lipid metabolism. Although the exact role of this protein in the liver is unclear, there is a large body of evidence that *PNPLA3* is associated with NAFLD.

In the landmark study for this field, a genome-wide association study (GWAS) resulted in the discovery of a single nucleotide polymorphism (SNP) in the gene