Viewpoint

Nonalcoholic fatty liver disease in obese adolescents: the role of genetic polymorphisms

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Nonalcoholic fatty liver disease (NAFLD) has recently become an emerging health problem worldwide (1). The pathogenetic mechanisms involved in the development and progression of NAFLD are due to genetic predisposition that expresses a metabolic profile associated with high energy food intake (2). The most accurate estimate of the worldwide prevalence of NAFLD is 24–25% of the general population, and ranges from 5–18% in Asia to 20–30% in the Western countries (1,3). Nowadays, the reason for this variability is not clear yet. However, it is plausible that genetic factors could play a major role in pathogenesis and the advances in genomics, transcriptomics, and proteomics have highlighted new pathogenic pathways. In fact, increasing literature data support the role of single nucleotide polymorphisms (SNPs), and in particular the SNPs of genes involved in insulin signaling, lipid homeostasis, and oxidative stress, not only in the susceptibility to develop NAFLD, but also in the severity of liver damage and in the etiology of multisystemic metabolic disorders (4). The development of the Genome Wide Association Study technology has allowed the identification of many SNPs involved in the onset of NAFLD, since they can change the stages of development, the rate of progression, and the efficacy of treatment (5). Recently, Tricò *et al*. investigate the clinical and genetic features associated with pediatric NAFLD in a prospective study in a large multiethnic cohort of obese adolescents (6). A total of 503 subjects, identified as "The Yale Pediatric NAFLD cohort", were enrolled, including 191 (38.0%) Caucasians, 134 (26.6%) African Americans, and 178 (35.4%) Hispanics. The participants underwent abdominal magnetic resonance imaging (MRI), oral glucose tolerance test, and the genotyping of three SNPs associated with fatty liver (rs738409 in the *PNPLA3* gene, rs1260326 in the *GCKR* gene, and rs58542926 in *TM6SF2* gene), to assess respectively hepatic fat accumulation, glucose tolerance, insulin sensitivity, and to evaluate the influence of the studied SNPs on the onset of NAFLD. The authors found that the prevalence of NAFLD in the cohort was 41.6%, and varied significantly between ethnicity and gender. In particular NAFLD was mainly detected by MRI in Hispanics and male patients. The authors observed also that African American obese adolescents have a lower prevalence of NAFLD. However, when fatty liver is detected, African American subjects showed a more severely impaired metabolic phenotype than patients from others ethnicities, with deep changes in insulin homeostasis and glucose metabolism. In addition, it is interesting to note that the study of major SNPs associated with NAFLD significantly increased the likelihood to predict changes in hepatic fat content and to predict the effects of fatty liver, on the basis of ethnicity.

In the era of personalized medicine, the study highlights how remarkably relevant the genetic background of an individual can be in predisposing to different metabolic disorders (4). The rs738409 SNP in the *PNPLA3* gene, for example, represents the only genetic variant currently associated to significant increase in the risk of developing both alcoholic liver disorders and NAFLD, and can affect insulin and glucose metabolism (4). Systemic assessment of the clinical impact of genetic and environmental factors, as reported by the authors in the Yale Pediatric NAFLD

cohort, provides indispensable tools to evaluate the actual contribution of single components of the pathogenesis of metabolic disorders and to identify efficient therapeutic approaches. Moreover, the study adds a longitudinal component that allows assessing the constant predisposing influence of the genetic background versus the variable effect of environmental factors, such as diet. The results are in line with other studies already addressing the beneficial role of dietary approaches (2), and confirm the importance of conducting large population studies like the one from Tricò *et al*. (6) in order to improve our knowledge of complex metabolic disorders, investigate the connection between apparently independently clinical entities, such as NAFLD and type 2 diabetes, and provide the best personalized treatment possible, based on elements of translational research and systems biology.

Considered the key role played in the onset of NAFLD, the development of a genetic approach to assess and non-invasively monitor liver disease progression, appear promising (7). Future research programs that integrate genomic, transcriptomic, proteomic, and metabolomic data are required to better manage and treat this disease. However, on the basis of the reported data, in agreement with the authors it is possible to conclude that the evaluation of SNPs associated to the study of changes in glucose blood levels might help identify obese adolescents at risk for developing fatty liver and its metabolic complications.

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Footnote

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