

Study identifies genetic variants linked to fatty liver disease in obese children

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New research found the genetic variant Patatin-like phospholipase domain containing protein-3 (PNPLA3) acting in conjunction with the glucokinase regulatory protein (GCKR) is associated with increased susceptibility to fatty liver disease in obese children. The study, published in the March issue of *Hepatology*, a journal of the American Association for the Study of Liver Diseases, determined the PNPLA3 and GCKR single nucleotide polymorphisms (SNPs) were responsible for up to 39% of the hepatic fat content in this pediatric population.

Obesity is a global health concern and children are not unscathed by this epidemic. As a result, experts say nonalcoholic [fatty liver disease](#) (NAFLD) is now the leading cause of [chronic liver disease](#) in children and adolescents in industrialized countries. Previous studies indicate genetics significantly impacts the susceptibility of developing fatty liver and [nonalcoholic steatohepatitis](#) (NASH), particularly in early-onset disease, which places greater interest on [childhood obesity](#).

For the current study, a team led by Dr. Nicola Santoro from Yale University School of Medicine in New Haven, Connecticut recruited 455 obese children and adolescents who underwent genotyping and fasting triglycerides and lipoprotein particles testing. Participants in this pediatric cohort had a mean age of 13 years with 181 Caucasian, 139 African American and 135 Hispanic children. Researchers measured hepatic fat content (HFF%) using [magnetic resonance imaging](#) (MRI) in a subset of 142 children.

Study findings show that rs1260326 in the GCKR gene is associated with higher triglycerides levels and higher levels of very-low-density lipoproteins (VLDL) in Caucasian and African American children. The GCKR SNP was associated with fatty liver in each of the three ethnic groups. A joint effect between PNPLA3 and GCKR SNPs was responsible for 32% of the HFF% in Caucasian, 39% in African American and 15% of Hispanic children. "Our findings confirm that obese youths with genetic variants in the GCKR and PNPLA3 genes may be more susceptible to fatty liver disease. We need to be cautious, though, and refrain to automatically extend this observation to the overall population. In fact, our data refer to a population of obese children and adolescents. I think that further studies involving lean subjects and adults may help to further define in more details these associations," said Dr. Santoro.

In a related editorial, Valerio Nobili with "Bambino Gesù" Children's Hospital and Research Institute in Italy concurs, "Dr. Santoro and colleagues determined the additive effect of PNPLA3 and GCKR variants explained over one third of hepatic fat content variance in obese children." He recommends that ethnicity data be replicated in larger study cohorts due to the small number of participants in each of the three groups.

The study authors suggest that the GCKR variant may lead to accumulation of fat in the liver through an increase in hepatic triglyceride production and further research is warranted to confirm their results. Dr. Santoro concludes, "While the small sample size raises the possibility of false negative results in our study, the presence of both GCKR and PNLPA3 genetic variants acting in combination confers susceptibility to fatty [liver disease](#) in obese children."

More information: "A Variant in the Glucokinase Regulatory Protein (GCKR) Gene is Associated with Fatty Liver in Obese Children and

Adolescents." Nicola Santoro, Clarence K. Zhang, Hongyu Zhao, Andrew J. Pakstis, Grace Kim, Romy Kursawe, Daniel J. Dykas, Allen E. Bale, Cosimo Giannini, Bridget Pierpont, Melissa M. Shaw, Leif Groop, Sonia Caprio. *Hepatology*; December 18, 2011 ([DOI: 10.1002/hep.24806](https://doi.org/10.1002/hep.24806)); Print Issue Date: March 2012.

Editorial: "Unraveling the genetics of fatty liver in obese children: additive effect of P446L GCKR and I148M PNPLA3 polymorphisms." Luca Valenti, Anna Alisi, Valerio Nobili. *Hepatology*; December 18, 2011 ([DOI: 10.1002/hep.25617](https://doi.org/10.1002/hep.25617)); Print Issue Date: March 2012.

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