Genetics of NAFLD: what we know so far

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Department of Pediatrics
Yale University

STOPNASH SYMPOSIUM
10/07/2015

Heritability of NAFLD

•Heritability of NAFLD in minority cohorts (African Americans and Hispanics was estimated to be 35%). **Wagenknecht LE et al. Obesity 2009**

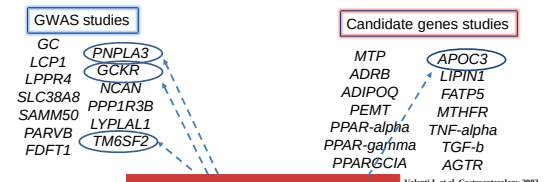
•Fatty liver is a complex disease, whose heritability has been estimated to be around 40%. **Schwimmer JB et al. Gastroenterology 2009**

•Heritability of hepatic fibrosis and steatosis based on a prospective twin study has been estimated to be about 50%. **Loomba R et al. Gastroenterology 2015**

35%---40%---50%

Gene Variants and NAFLD

Gene variants associated with Intra-hepatic fat content by GWAS and hypothesis driven studies



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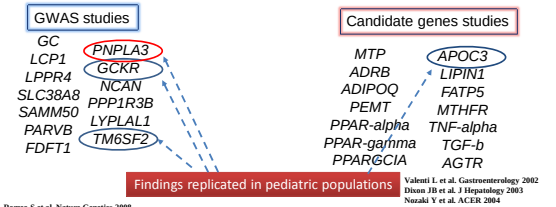

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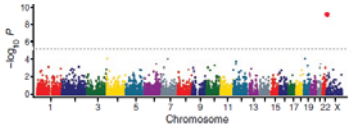
Valenti et al. JPGN 2012
Peng XE et al. Liver Int. 2013

Role of *PNPLA3* in NAFLD

Genetic variation in *PNPLA3* confers susceptibility to nonalcoholic fatty liver disease

Stefano Romeo[1,8], Julia Kozlitina[2,3,8], Chao Xing[1,2], Alexander Pertsemlidis[1], David Cox[4], Len A Pennacchio[5], Eric Boerwinkle[6], Jonathan C Cohen[1] & Helen H Hobbs[1,7]



The non-synonymous SNP rs738409 in the *PNPLA3* is characterized by a C to G substitution encoding an isoleucine to methionine substitution at the amino acid position 148

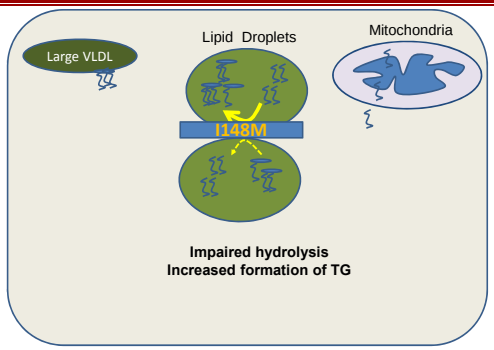
Romeo et al. Nat Genet 2008

Role of *PNPLA3* in NAFLD

The Patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) also known as adiponutrin (ADPN), is expressed in the liver and in the adipose tissue and has both triacylglycerol hydrolase and acyglycerol transacetylase activity.

Romeo et al. Nat Genet 2008

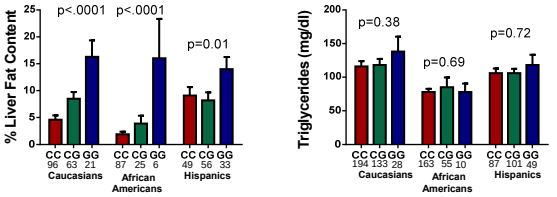
Role of *PNPLA3 rs738409* in NAFLD



Perttilä J et al. AJPEM. 2012; 302: E1063-9
Kumari M et al Cell Metab. 2012;15:691-702

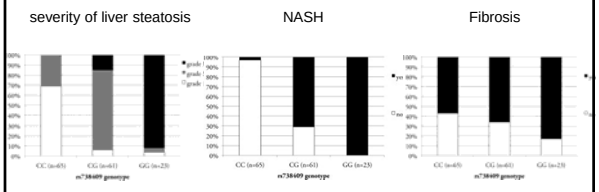
Huang Y et al J Biol Chem. 2011; 286: 37085-93.
Li JZ et al. J Clin Invest. 2012;122: 4130-44.
Smagris E et al Hepatology 2015

PNPLA3 rs738409 Hepatic fat content and Triglycerides



Modified from Santoro N et al. Hepatology 2010 and Santoro N et al. Hepatology 2012

I148M patatin-like phospholipase domain-containing 3 gene variant and severity of pediatric nonalcoholic fatty liver disease



Valenti L et al Hepatology 2010

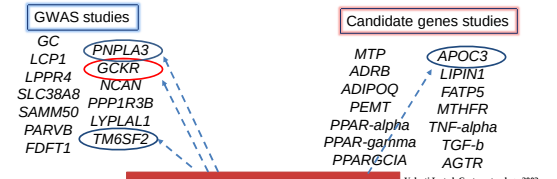
The *PNPLA3 rs738409* SNP modulate the degree of liver injury in other hepatic diseases

- Liver injury in NAFLD
- Alcoholic Fatty Liver Disease
- Liver damage in HBV and HCV
- Hepatocellular carcinoma in non-viral hepatitis
- NASH and Fibrosis in HIV-1-Monoinfected Adults
- Reduces Survival of patients with primary Sclerosing Cholangitis
- Liver damage in subjects with Inflammatory Bowel Disease
- Favors the onset of fibrosis in subjects with Hemochromatosis.

Tian C et al. Nature Genetics 2010
Nischalke HD et al. PloS One 2011
Krawczyk M et al. J Hepatology 2015
Mandorfer M et al. Liver Int 2015
Friedrich Ket al. PloS One 2013
Mancina RM et al. Inflam Bowel Dis 2015
Valenti L et al. W J Hepatology 2015

Gene Variants and NAFLD

Gene variants associated with Intra-hepatic fat content by GWAS and hypothesis driven studies



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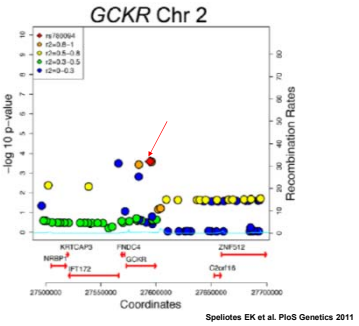
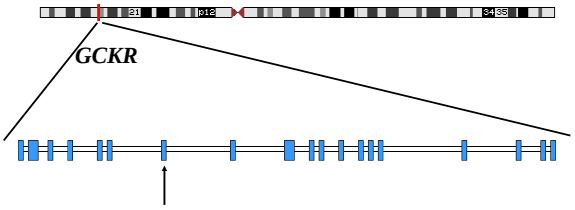
GCKR gene and NAFLD



Speliotes EK et al. PloS Genetics 2011

GCKR gene and NAFLD

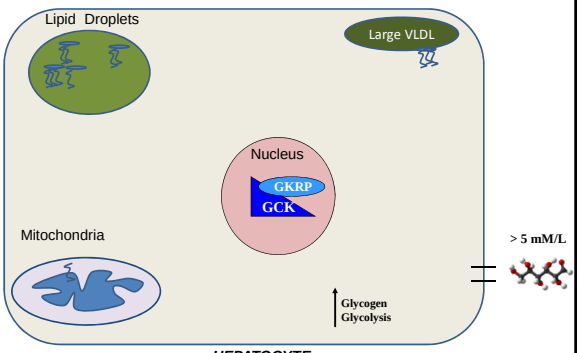
Chromosome 2p23.3



GCKR

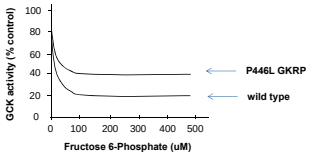
rs1260326
C1337T
(P446L)

GCKR gene and NAFLD

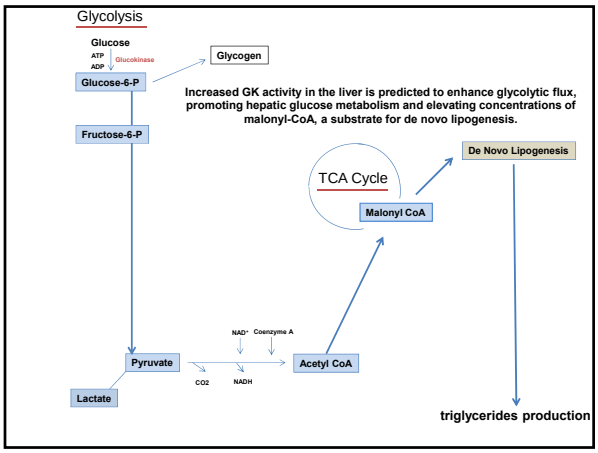


GCKR gene and NAFLD

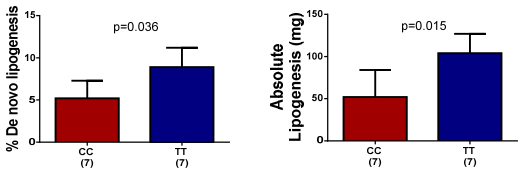
The binding affinity between GKRP for GK is reduced in subjects carrying the risk allele



Modified from Hum Mol Genet. 2009; 18: 4081-8.

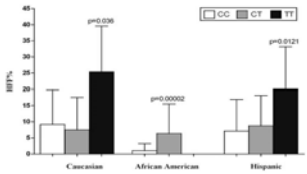


Fasting DNL% and Absolute Lipogenesis According to the *GCKR* 1260326 genotype



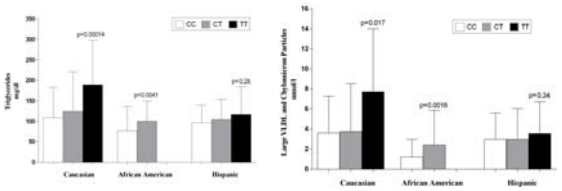
Modified from Santoro N et al. JCEM 2015

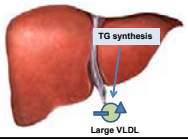
GCKR rs1260326 Phenotype



Santoro N et al. Hepatology 2012

GCKR rs1260326 Phenotype





Santoro N et al. Hepatology 2012

Gene Variants and NAFLD

Gene variants associated with Intra-hepatic fat content by GWAS and hypothesis driven studies

GWAS studies

GC
LCP1
LPPR4
SLC38A8
SAMM50
PARVB
FDFT1
PNPLA3
GCKR
NCAN
PPP1R3B
LYPLAL1
TM6SF2

Candidate genes studies

MTP
ADRB
ADIPOQ
PEMT
PPAR-alpha
PPAR-gamma
PPARGCIA
APOC3
LIPIN1
FATP5
MTHFR
TNF-alpha
TGF-b
AGTR

Findings replicated in pediatric populations

Romeo S et al. Nature Genetics 2008
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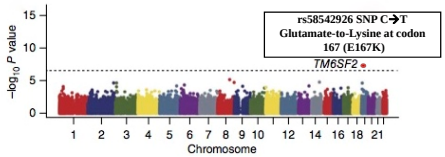
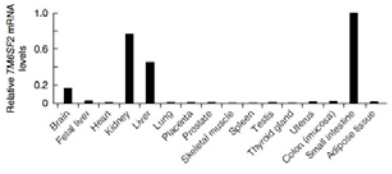
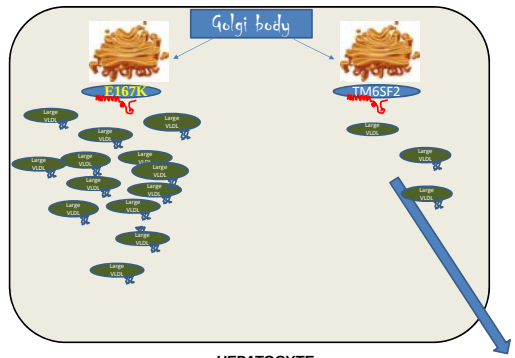
TM6SF2 gene and NAFLD





Kozlitina, J., et al. Nat Genet, 2014

TM6SF2 gene and NAFLD



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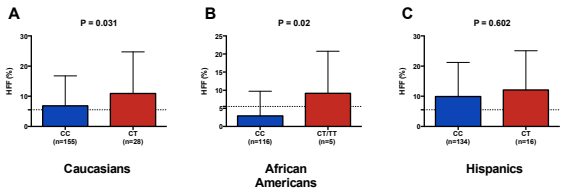

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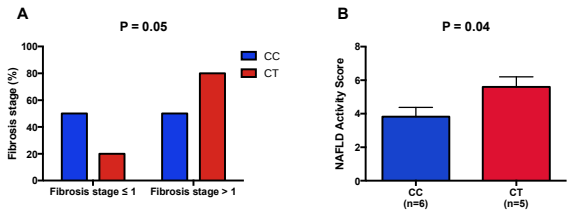
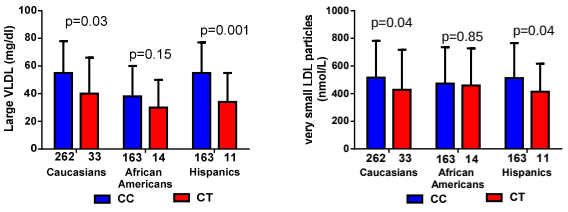
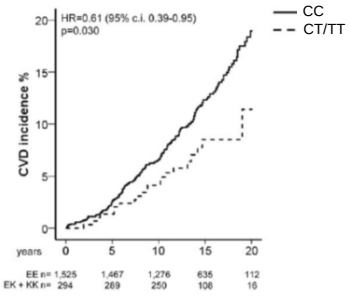


TM6SF2 gene and NAFLD



TM6SF2 gene and CVD Risk



Modified from Dongiovanni P et al. Hepatology 2015

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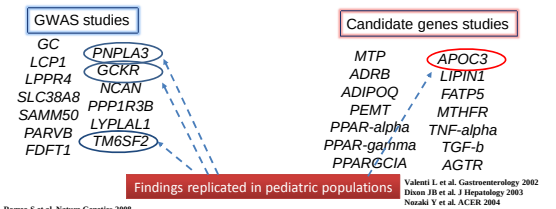

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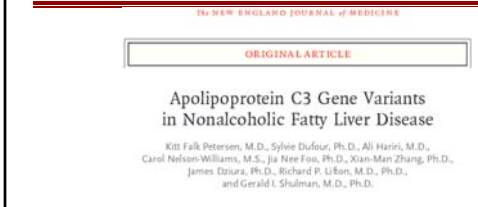
APOC3 gene and NAFLD


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

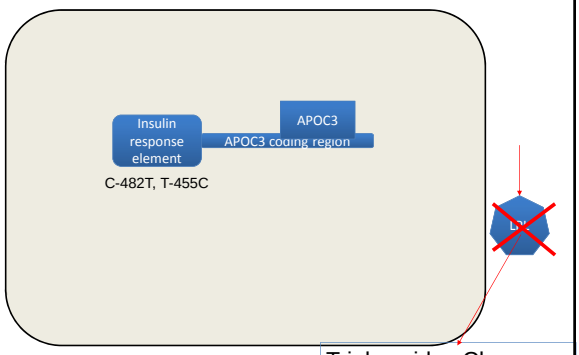
Apolipoprotein C3 Gene Variants in Nonalcoholic Fatty Liver Disease

Kitt Falk Petersen, M.D., Sylvie Dufour, Ph.D., Ali Hariri, M.D., Carol Nelson-Williams, M.S., Jia Nee Foo, Ph.D., Xian-Man Zhang, Ph.D., James Dziura, Ph.D., Richard P. Lifton, M.D., Ph.D., and Gerald I. Shulman, M.D., Ph.D.

Two SNPs, C-482T and T-455C, in complete LD, in the insulin response element of the APOC3 gene.

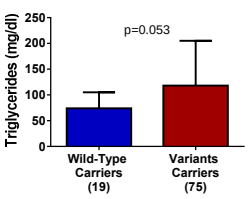
Petersen KF et al. N Engl J Med. 2010

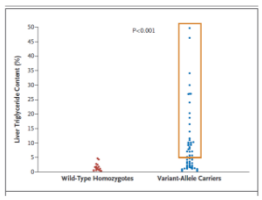
APOC3 gene and NAFLD



APOC3 gene and NAFLD

As a result, carriers of the APOC3 risk alleles have increased hepatic uptake of lipids from chylomicron remnants, predisposing them to nonalcoholic fatty liver disease



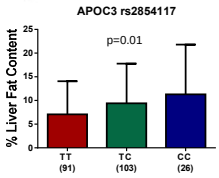


Petersen KF et al. N Engl J Med. 2010

APOC3 gene and NAFLD

Genetic and Clinical Markers of Elevated Liver Fat Content in Overweight and Obese Hispanic Children

Ryan W. Walker[1], Frank Sinatra[2], Jaana Hartiala[1], Marc Weigensberg[1], Donna Spruijt-Metz[1], Tanya L. Alderete[1], Michael I. Goran[1] and Hooman Allayee[1]

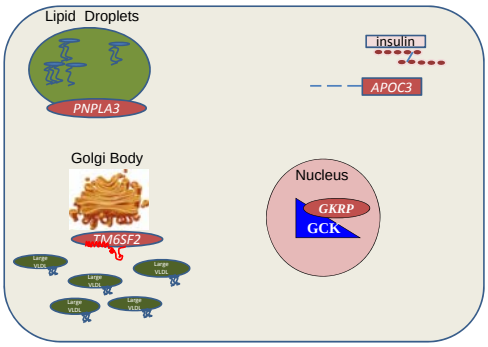


Modified from Walker RW et al. Obesity 2013

SNPs reproducibly associated with pediatric Fatty Liver

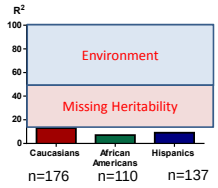
Gene	SNP	Function	Hepatic Fat	Circulating lipids
PNPLA3	rs738409	remodeling of lipid droplets	↑	=
GCKR	rs1260326	modulation of hepatic lipogenesis	↑	↑
TM6SF2	rs58542926	modulation lipoprotein secretion	↑	↓
APOC3 *	rs2854117	modulation TGs clearance	↑	↑

* Association found in Asian Indians and Hispanics



How much variance of intra-hepatic fat content do these variants explain in the pediatric population?

PNPLA3 rs738409
GCKR rs1260326
TM6SF2 rs58542926
APOC3 rs2854117



n=176 n=110 n=137

About 40% of NAFLD heritability remains unexplained

Summary

- GWAS and candidate genes studies have allowed to discover gene variants associated with NAFLD, but only few of those have been replicated in pediatric populations.
- These studies have allowed to learn about genes, whose function was unknown.
- The majority of the SNPs associated to NAFLD is in genes involved in lipid metabolism.
- Altogether, the gene variants reproducibly associated with NAFLD in the pediatric population explain just a small fraction of NAFLD heritability.
- There is need for more genetic studies to discover new variants that may lead to the discovery of novel mechanisms underlying the pathogenesis of NAFLD.

Acknowledgments

Patients and their families
HRU Staff Yale New Haven Hospital

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Sonia Caprio
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Elizabeth J. Parks

YALE PUBLIC HEALTH
Hongyu Zhao

YALE GENETICS
Allen E. Bale
Daniel J. Dykas

UC SAN DIEGO
Ariel E. Feldstein

LUND UNIVERSITY
Leif Groop

Yale Center for Clinical Investigation

American Heart Association
Learn and Live

American Diabetes Association.