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# *PNPLA3* Polymorphisms and Liver Aminotransferase Levels in a Mexican American Population

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## Abstract

**Objective—**This study examined genetic associations of *PNPLA3* polymorphisms and liver aminotransferases in an extensively documented, randomly recruited Mexican American population at high risk of liver disease.

**Methods—**Two single nucleotide polymorphisms (SNP) in the *PNPLA3* gene, i.e. rs738409 and rs2281135, were genotyped in 1532 individuals. Population stratification was corrected by the genotyping of 103 ancestry informative markers (AIMs) for Mexican Americans.

**Results—**Both *PNPLA3* SNPs showed highly significant association with alanine aminotransferase (ALT) levels, but was also in males associated with aspartate aminotransferase (AST) levels. Haplotypic association test of the two SNPs suggested stronger genetic association with rs738409 than rs2281135. Obvious sex effects were characterized: rs738409-sex interaction in ALT levels had $P=8.37\times10^{-4}$; rs738409-sex interaction in AST levels had $P=5.03\times10^{-3}$.

**Conclusions—**This population study highlights a sex-specific association of *PNPLA3* polymorphisms and elevated liver enzymes in a population-based study, independent of common pathological factors of the metabolic syndrome. The strong genetic association found in

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**Author Contributions:** Quan Li researched data, reviewed/edited the manuscript. Hui-Qi Qu conceived the study, researched the data, and wrote the manuscript. Megan L Grove and Yang Lu performed the experiments. Anne R Rentfro, Shaper Mirza, Michael B Fallon, Craig L Hanis, and Eric Boerwinkle, reviewed/edited the manuscript. Susan P Fisher-Hoch and Joseph B McCormick conceived the study and wrote the manuscript.

women≤50 years old, but not in women>50 years old, suggests that sex hormones may mediate the sex effect.

### Keywords

alanine aminotransferase; sex; genetic association; plasma liver enzymes; *PNPLA3*; metabolic syndrome; single nucleotide polymorphism

## Introduction

The Hispanic population and Mexican Americans in particular, not only have high rates of obesity, diabetes and the metabolic syndrome, but also liver disease, particularly non-alcoholic fatty liver disease (NAFLD) [1,2,3,4,5]. The patatin-like phospholipase domain containing 3 gene (*PNPLA3*) at Chr22q13.31 was originally identified in adipose tissue by Baulande et al. and named adiponutrin [6]. This gene is specifically expressed in adipose tissue and is under tight nutritional regulation [6]. What implicates *PNPLA3* in liver disease is that, in 2008, Romeo et al. identified an association between an amino acid substitution I[Ile]148M[Met] (NCBI dbSNP ID: rs738409) in the *PNPLA3* gene and genetic susceptibility for NAFLD [7]. This observation was confirmed in a number of subsequent reports [8,9,10,11,12,13]. Recent functional experiments showed that the I148M substitution from SNP rs738409 caused a loss of function of its enzymatic activity [14]. Studies also showed an association of *PNPLA3* variations with increased plasma levels of liver enzymes [15,16]. The strongest signal of the quantitative trait association was tagged by the SNP rs2281135. Genetic association of a *PNPLA3* variant with alcoholic liver disease was also proposed [17]. Together these interesting observations suggested *PNPLA3* might encode a key molecule mediating the pathological processes of liver injury in metabolic disorders.

Given the high rate of NAFLD in Hispanics we examined the genetic association of *PNPLA3* SNPs and liver enzymes in a cohort of Mexican Americans randomly recruited in the community: the Cameron County Hispanic Cohort (CCHC) in the Lower Rio Grande Valley (LRGV) in south Texas, US [18]. The participants of this cohort were randomly recruited in the city of Brownsville, Cameron County, based on 2000 Census tract data. In this population we observe a 49.5% prevalence of obesity and a 30.7% prevalence of diabetes, and abnormal serum liver enzymes are common[3,19,20]. Assessing the genetic effect of *PNPLA3* variants in this population may lead to further understanding of genetic drivers of liver injury in this underserved minority population.

## Methods

### 1. Subjects

This study investigated 1532 individuals from the CCHC cohort. The characteristics of this cohort have been extensively described in previous reports [18,19,21]. The participants were randomly selected from the population and no disease criteria were applied in their selection. Therefore, the participants are representative of the general population. Blood samples were obtained at recruitment. Informed consent was obtained from each individual, and the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston (UTHealth) approved this study.

### 2. Genotyping

The genotyping for this study was done using the Sequenom iPLEX assay (Sequenom, Cambridge, MA).Two single nucleotide polymorphisms (SNP) in the *PNPLA3* gene, i.e. rs738409 and rs2281135, were genotyped. rs738409 was the SNP I148M that was originally

identified as having genetic association with NAFLD[7]. The other SNP rs2281135 was identified as the strongest association in this genetic region with elevated ALT by a genome-wide association study in a European population[15]. As is shown by HapMap data, rs738409 and rs2281135 are in tight linkage disequilibrium (LD) in three major human ethnic groups: African, Caucasian, and East Asian (Table 1). The genotyping call rates of both SNPs were 100%. The Mexican Americans in our study are an admixed population, predominantly with European and Native American ancestry. To address the potential bias of population stratification, we genotyped 103 continental ancestry informative markers (AIMs) for Mexican Americans identified by a previous study [22]. All these AIMs are on auto-chromosomes. The genotyping call rates of the 103 AIM SNPs were between 95.4%~100%, with a median of 99.9%. For the purpose of quality control, 93 DNA samples were genotyped in duplicate. The concordance rate of each duplicate was 100%.

### 3. Statistical methods

The population structure of the Mexican American population was analyzed by principal component analysis using the Eigensoft version 2.0 software (19). Quantitative trait association tests were performed using PLINK software (http://pngu.mgh.harvard.edu/~purcell/plink/). The additive genetic model was used in the association test. All association test results were adjusted for age. CCHC participants showed the predominant one-dimensional character of the admixture of European and American Indian ancestries. The first principal component (PC1) explained the majority of population structure. Therefore, all association test results in this study were corrected for PC1.

## Results

Sex difference in liver injury was observed in our previous epidemiological analyses of this population [3,19]. Previous studies have also suggested a possibility of sex difference in the genetic association of *PNPLA3* and liver enzymes[23]. In our study, we observed significant sex-SNP interaction: rs738409-sex interaction in ALT levels had $P=8.37\times10^{-4}$; rs738409-sex interaction in AST levels had $P=5.03\times10^{-3}$. Therefore, genetic effects were assessed in males and females respectively in this study. By the quantitative trait association test, *PNPLA3* SNPs showed highly significant association with ALT levels in both males and females (Table 2). Association between the *PNPLA3* SNPs and AST levels was also statistically significant in males, however the genetic association between the *PNPLA3* SNPs and AST levels was not seen in females. The sex difference in AST association has a statistical significance of $p=0.024$ for rs738409, and $p=0.055$ for rs2281135.

Table 1 shows that two *PNPLA3* SNPs rs738409 and rs2281135 are in tight linkage disequilibrium (LD) in Mexican Americans similar to that seen in three other major human ethnic groups: African, Caucasian, and East Asian (Table 1). The genetic association was replicated in haplotypic association tests (Table 3). As shown by the haplotypic association tests, the direction of the genetic effect of two haplotypes carrying the same C allele of rs738409 is the same, but this is not the case for the two haplotypes carrying the same C allele of rs2281135. The ALT associations of the rs738409–rs2281135 haplotypes C-C *vs.* G-C are heterogeneous with highly statistical significances ($p=2.97\times10^{-5}$ in males, and $p=5.89\times10^{-6}$ in females). The AST associations of the two haplotypes were also heterogeneous with statistical significances ($p=2.36\times10^{-5}$ in males, and $p=0.076$ in females).

To further examine the sex effect we performed step-wise logistic regression analysis by taking series of cutoffs of ALT or AST values for classification (Table 4). With age and population structure corrected, the logistic regression analysis also suggested a sex effect.

Interestingly, using the traditionally cutoff of over 40U/L denoting elevated ALT, the association of rs738409 or rs2281135 with elevation was not significant in males ($p$=0.187 for rs738409, $p$=0.164 for rs2281135), but was highly significant in females ($p = 1.72 \times 10^{-5}$ for rs738409, $p = 1.30 \times 10^{-5}$ for rs2281135). Rather highly statistical significance was seen in the logistic regression using a higher cutoff value in males. The *PNPLA3* SNP rs738409 have stronger association with considerably more elevated ALT levels in males than that in females. A similar trend towards much higher elevation in males was also observed in the association with AST levels.

As we have already shown in this Mexican American population, obesity, insulin resistance, and the metabolic syndrome (MetS) are common [3,19]. We have also shown that in this population the ratio between plasma levels of two key adipokines, adiponectin and leptin is critical in MetS[21]. To determine how these metabolic disorders might be related to the genetic association of *PNPLA3* polymorphisms and liver enzymes, we tested the association between the *PNPLA3* SNPs and Body Mass Index (BMI), the homeostasis model assessment-estimated insulin resistance (HOMA-IR), adiponectin, leptin, and Log(leptin/adiponectin). With age and population structure corrected, no genetic association was identified between *PNPLA3* polymorphisms and BMI, HOMA-IR, adiponectin, and leptin (Table 5).

The genetic association of rs738409 and ALT in women≤50 years old versus women>50 years old were then compared, to test the theory that sex hormone levels may be responsible for gender differences. Although not measured in these subjects, it is assumed that there are significant differences in estrogen levels in these two age groups. A strong genetic association was found in women≤50 years old ($\beta$=0.202, $P=1.69\times10^{-7}$), but not in women>50 years old ($\beta$ =0.060, P=0.231).

## Discussion

We show in this study that genetic association between *PNPLA3* polymorphisms and elevated plasma liver enzymes is highly statistically significant in a Mexican American population. We also show that population structure of this admixed sample has no obvious effect on this association. Furthermore, the haplotypic association test suggests the genetic association tagged by the two *PNPLA3* SNPs represents a single genetic effect. Interestingly, we observed a sex effect of *PNPLA3* polymorphisms, which was therefore characterized in detail in this Mexican American population.

Phospholipase $A_2$ ($PLA_2$) catalyzes the hydrolysis of the sn-2 position of membrane glycerophospholipids to liberate arachidonic acid (AA) and produce lysophospholipids [24]. AA is a precursor of eicosanoids including prostaglandins (PGs) and leukotrienes (LTs). Lysophospholipids are potent biologically active lipid mediators that exert a wide range of cellular effects through specific G protein-coupled receptors [25]. In the $PLA_2$ enzyme superfamily, six families of $PLA_2$ with different action mechanisms and biological activities have been identified [26]. *PNPLA3* encodes a member of the Calcium-Independent $PLA_2$ ($iPLA_2$) family. The $iPLA_2$ enzymes have been known to play a major role in membrane phospholipid remodeling [27]. *PNPLA3* was originally identified in adipose tissue as Adiponutrin [6], where its expression is under tight nutritional regulation. In the fasting status, *PNPLA3* mRNA is almost undetectable, but increases dramatically after a high carbohydrate challenge [6]. Studies have shown triacylglycerol (TAG) lipase activity and acylglycerol transacylase activity of the *PNPLA3* protein [28]. Important insight into *PNPLA3* involvement in liver lipid metabolism comes from the most recent genetic studies. The derived allele of SNP rs738409 in *PNPLA3* was found to be associated with increased liver fat content [7,13], NAFLD [7,8,9,10,11,12,13], and increased plasma levels of liver

enzymes [15,16]. Functional experiment showed that the I148M substitution from SNP rs738409 caused a loss of function of its enzyme activity[14].

Prior to our study, a meta-analysis by Sookoian and Pirola suggested the possibility of sex difference in the genetic association of *PNPLA3* polymorphisms and liver enzymes; that is a negative association between the effect of rs738409 on liver fat content and male sex using meta-regression analysis [23]. Our study confirms and advances this observation by showing that the *PNPLA3* SNPs have stronger association with more highly elevated ALT levels in males, but lack of association with moderately elevated ALT in males. A recent report by Huang et al. showed that, in mice, nutritional control of *PNPLA3* expression in liver was regulated by a feed-forward loop that couples transcriptional and posttranslational controls. The transcription factor SREBP-1c plays key roles by directly activating *Pnpla3* transcription and indirectly inhibiting PNPLA3 degradation through the stimulation of fatty acid synthesis [29]. Transcription of *PNPLA3* is regulated by the transcription factor, sterol regulatory element binding protein 1c (SREBP-1c)[29]. SREBP-1c is a direct target gene of the liver X receptor (LXR) /retinoid X receptor (RXR) heterodimer [30]. Transcriptional regulation of *PNPLA3* by fasting and refeeding requires both SREBP-1c and LXR/RXR [29]. Estrogen can cause down-regulation of expression of both LXR and SREBP-1c [31]. This sex hormone mediated mechanism may explain the interesting sex effect characterized in this study.

In human adipose tissue, *PNPLA3* mRNA expression is also observed to be regulated by energy intake. *PNPLA3* mRNA levels have not been found to be different between non-obese and obese women, and do not correlate with adiposity indexes or leptin or adiponectin mRNAs [32]. Our data provides further evidence that obesity, insulin resistance, and adipose disorder, are not involved in this genetic association of liver enzymes. Although MetS has a high prevalence and is the major common factor in liver injury in our population[3,21], our data suggest *PNPLA3*-mediated liver enzyme change is independent of these common pathological factors of MetS.

To our knowledge, this is the first study of the genetic association of *PNPLA3* polymorphisms and liver enzymes using material from a community cohort in a small US minority city with homogenous culture and life-style. This homogeneity makes this population a unique resource for biomarker studies [19,21]. Besides the genetic effect of *PNPLA3* polymorphism, we identified a number of other factors involved in elevated liver enzymes in this population, including plasma insulin level and insulin resistance, BMI and body weight, serum triglycerides and non-HDL cholesterol, and hypertension. After correction for these factors, we demonstrated that the genetic effect from *PNPLA3* polymorphism is independent (e.g. rs738409 and ALT levels $P=2.00\times10^{-7}$)[33]. Our study has limitations. Diet is a risk factor of NAFLD. However, we don't have a robust method to measure diet in this community population. We did not identify the association of the *PNPLA3* variant and AST in females. Plasma AST level lacks specificity for liver injury, as AST is found widely in multiple tissues: red blood cells, liver, heart, muscle tissue, pancreas, and kidneys. Although we identified an interesting sex-specific effect of the *PNPLA3* variant, we could not further clarify underlying mechanisms. We speculate that sex hormone may mediate the sex effect, however we do not currently have data concerning plasma sex hormone levels in our cohort participants. Trying to partially compensate for this, we compared the genetic association of rs738409 and ALT in women≤50 years old *versus* women>50 years old. The age effect in women result suggests that, if sex hormones are involved in liver injury, endogenous estrogen is not protective either in liver injury in women.

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## Abbreviations

| | |
|---|---|
| **ALT** | alanine aminotransferase |
| **AIMs** | ancestry informative markers |
| **AST** | aspartate aminotransferase |
| **BMI** | Body Mass Index |
| **CCHC** | Cameron County Hispanic Cohort |
| **HOMA-IR** | homeostasis model assessment-estimated insulin resistance |
| **LD** | linkage disequilibrium |
| **MetS** | metabolic syndrome |
| **NAFLD** | non-alcoholic fatty liver disease |
| **PNPLA3** | patatin-like phospholipase domain containing 3 gene |
| **SNP** | single nucleotide polymorphisms |

## References

1. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40:1387–1395. [PubMed: 15565570]
2. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int. 2009; 29:113–119. [PubMed: 18384521]
3. Pan JJ, Qu HQ, Rentfro A, McCormick JB, Fisher-Hoch SP, Fallon MB. Prevalence of metabolic syndrome and risks of abnormal serum alanine aminotransferase in Hispanics: a population-based study. PLoS One. 2011; 6:e21515. [PubMed: 21720553]
4. Perez A, Anzaldua M, McCormick J, Fisher-Hoch S. High frequency of chronic end-stage liver disease and hepatocellular carcinoma in a Hispanic population. J Gastroenterol Hepatol. 2004; 19:289–295. [PubMed: 14748876]
5. Weston SR, Leyden W, Murphy R, Bass NM, Bell BP, Manos MM, Terrault NA. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. Hepatology. 2005; 41:372–379. [PubMed: 15723436]
6. Baulande S, Lasnier F, Lucas M, Pairault J. Adiponutrin, a transmembrane protein corresponding to a novel dietary- and obesity-linked mRNA specifically expressed in the adipose lineage. J Biol Chem. 2001; 276:33336–33344. [PubMed: 11431482]

7. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008; 40:1461–1465. [PubMed: 18820647]
8. Sookoian S, Castano GO, Burgueno AL, Gianotti TF, Rosselli MS, Pirola CJ. A nonsynonymous gene variant in the adiponutrin gene is associated with nonalcoholic fatty liver disease severity. J Lipid Res. 2009; 50:2111–2116. [PubMed: 19738004]
9. Valenti L, Alisi A, Galmozzi E, Bartuli A, Del Menico B, Alterio A, Dongiovanni P, Fargion S, Nobili V. I148M patatin-like phospholipase domain-containing 3 gene variant and severity of pediatric nonalcoholic fatty liver disease. Hepatology. 2010; 52:1274–1280. [PubMed: 20648474]
10. Valenti L, Al-Serri A, Daly AK, Galmozzi E, Rametta R, Dongiovanni P, Nobili V, Mozzi E, Roviaro G, Vanni E, Bugianesi E, Maggioni M, Fracanzani AL, Fargion S, Day CP. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology. 2010; 51:1209–1217. [PubMed: 20373368]
11. Speliotes EK, Butler JL, Palmer CD, Voight BF, Hirschhorn JN. PNPLA3 variants specifically confer increased risk for histologic nonalcoholic fatty liver disease but not metabolic disease. Hepatology. 2010; 52:904–912. [PubMed: 20648472]
12. Rotman Y, Koh C, Zmuda JM, Kleiner DE, Liang TJ. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology. 2010; 52:894–903. [PubMed: 20684021]
13. Kotronen A, Johansson LE, Johansson LM, Roos C, Westerbacka J, Hamsten A, Bergholm R, Arkkila P, Arola J, Kiviluoto T, Fisher RM, Ehrenborg E, Orho-Melander M, Ridderstrale M, Groop L, Yki-Jarvinen H. A common variant in PNPLA3, which encodes adiponutrin, is associated with liver fat content in humans. Diabetologia. 2009; 52:1056–1060. [PubMed: 19224197]
14. Huang Y, Cohen JC, Hobbs HH. Expression and characterization of a PNPLA3 protein isoform (I148M) associated with nonalcoholic fatty liver disease. J Biol Chem. 2011; 286:37085–37093. [PubMed: 21878620]
15. Yuan X, Waterworth D, Perry JRB, Lim N, Song K, Chambers JC, Zhang W, Vollenweider P, Stirnadel H, Johnson T, Bergmann S, Beckmann ND, Li Y, Ferrucci L, Melzer D, Hernandez D, Singleton A, Scott J, Elliott P, Waeber G, Cardon L, Frayling TM, Kooner JS, Mooser V. Population-Based Genome-wide Association Studies Reveal Six Loci Influencing Plasma Levels of Liver Enzymes. The American Journal of Human Genetics. 2008; 83:520–528.
16. Kollerits B, Coassin S, Kiechl S, Hunt SC, Paulweber B, Willeit J, Brandstätter A, Lamina C, Adams TD, Kronenberg F. A common variant in the adiponutrin gene influences liver enzyme values. Journal of Medical Genetics. 2010; 47:116–119. [PubMed: 19542081]
17. Tian C, Stokowski RP, Kershenobich D, Ballinger DG, Hinds DA. Variant in PNPLA3 is associated with alcoholic liver disease. Nat Genet. 2010; 42:21–23. [PubMed: 19946271]
18. Fisher-Hoch SP, Rentfro AR, Salinas JJ, Perez A, Brown HS, Reininger BM, Restrepo BI, Wilson JG, Hossain MM, Rahbar MH, Hanis CM, McCormick JB. Socioeconomic status and prevalence of obesity and diabetes in a Mexican American community, Cameron County, Texas, 2004–2007. Prev Chronic Dis. 2010; 7:A53. [PubMed: 20394692]
19. Qu HQ, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. PLoS One. 2011; 6:e21041. [PubMed: 21695082]
20. Qu HQ, Rentfro AR, Lu Y, Nair S, Hanis CL, McCormick JB, Fisher-Hoch SP. Host susceptibility to tuberculosis: insights from a longitudinal study of gene expression in diabetes. Int J Tuberc Lung Dis. 2012
21. Mirza S, Qu HQ, Li Q, Martinez PJ, Rentfro AR, McCormick JB, Fisher-Hoch SP. Adiponectin/leptin ratio and metabolic syndrome in a Mexican American population. Clin Invest Med. 2011; 34:E290. [PubMed: 21968271]
22. Kosoy R, Nassir R, Tian C, White PA, Butler LM, Silva G, Kittles R, Alarcon-Riquelme ME, Gregersen PK, Belmont JW, De La Vega FM, Seldin MF. Ancestry informative marker sets for determining continental origin and admixture proportions in common populations in America. Hum Mutat. 2009; 30:69–78. [PubMed: 18683858]

23. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology. 2011; 53:1883–1894. [PubMed: 21381068]
24. Murakami M, Kudo I. Phospholipase A2. J Biochem. 2002; 131:285–292. [PubMed: 11872155]
25. Rivera R, Chun J. Biological effects of lysophospholipids. Rev Physiol Biochem Pharmacol. 2008; 160:25–46. [PubMed: 18481029]
26. Dennis EA, Cao J, Hsu YH, Magrioti V, Kokotos G. Phospholipase A2 enzymes: physical structure, biological function, disease implication, chemical inhibition, and therapeutic intervention. Chem Rev. 2011; 111:6130–6185. [PubMed: 21910409]
27. Winstead MV, Balsinde J, Dennis EA. Calcium-independent phospholipase A(2): structure and function. Biochim Biophys Acta. 2000; 1488:28–39. [PubMed: 11080674]
28. Jenkins CM, Mancuso DJ, Yan W, Sims HF, Gibson B, Gross RW. Identification, cloning, expression, and purification of three novel human calcium-independent phospholipase A2 family members possessing triacylglycerol lipase and acylglycerol transacylase activities. J Biol Chem. 2004; 279:48968–48975. [PubMed: 15364929]
29. Huang Y, He S, Li JZ, Seo YK, Osborne TF, Cohen JC, Hobbs HH. A feed-forward loop amplifies nutritional regulation of PNPLA3. Proc Natl Acad Sci U S A. 2010; 107:7892–7897. [PubMed: 20385813]
30. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL, Mangelsdorf DJ. Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. Genes Dev. 2000; 14:2819–2830. [PubMed: 11090130]
31. D'Eon TM, Souza SC, Aronovitz M, Obin MS, Fried SK, Greenberg AS. Estrogen regulation of adiposity and fuel partitioning, Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. J Biol Chem. 2005; 280:35983–35991. [PubMed: 16109719]
32. Liu YM, Moldes M, Bastard JP, Bruckert E, Viguerie N, Hainque B, Basdevant A, Langin D, Pairault J, Clement K. Adiponutrin: A new gene regulated by energy balance in human adipose tissue. J Clin Endocrinol Metab. 2004; 89:2684–2689. [PubMed: 15181042]
33. Qu HQ, Li Q, Grove ML, Lu Y, Pan JJ, Rentfro AR, Bickel PE, Fallon MB, Hanis CL, Boerwinkle E, McCormick JB, Fisher-Hoch SP. Population-based risk factors for elevated alanine aminotransferase in a South Texas Mexican American Population. 2012 Submitted.

**Table 1**

Linkage disequilibrium of the two *PNPLA3* SNPs associated with ALT/AST levels

| Population* | rs738409 (minor allele, frequency) | rs2281135 (minor allele, frequency) | LD of rs738409-rs2281135 (D', $r^2$) |
|---|---|---|---|
| CEU | G, 0.233 | T, 0.208 | 0.839, 0.609 |
| YRI | G, 0.125 | T, 0.158 | 0.920, 0.643 |
| CHB+JPT | G, 0.388 | T, 0.388 | 0.976, 0.953 |
| CCHC | G, 0.495 | T, 0.468 | 0.983, 0.832 |

* The abbreviations represent: YRI, Yoruba in Ibadan, Nigeria; CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; JPT, Japanese in Tokyo, Japan; CHB, Han Chinese in Beijing, China. These reference populations were genotyped in the HapMap study (http://www.hapmap.org).

**Table 2**

Quantitative trait association test between *PNPLA3* polymorphisms and ALT/AST levels

| Trait | SNP | Males(n=496) | | | Females (n=1036) | | |
|---|---|---|---|---|---|---|---|
| | (reference allele) | Regression coefficient (β, U/L) | Standard error (SE) | *P* | Regression coefficient (β, U/L) | Standard error (SE) | *P* |
| ALT | rs738409 (C) | 7.517 | 1.591 | $2.99 \times 10^{-6}$ | 2.970 | 0.658 | $7.10 \times 10^{-6}$ |
| ALT | rs2281135 (T) | 7.202 | 1.635 | $1.30 \times 10^{-5}$ | 2.542 | 0.658 | $1.18 \times 10^{-4}$ |
| AST | rs738409 (C) | 4.589 | 1.208 | $1.64 \times 10^{-4}$ | 0.987 | 0.663 | 0.137 |
| AST | rs2281135 (T) | 3.996 | 1.243 | $1.40 \times 10^{-3}$ | 0.833 | 0.661 | 0.208 |

**Table 3**

Haplotypic association test between *PNPLA3* variant and ALT/AST levels

| Trait | Haplotype (rs738409-rs2281135) | Males(n=496) | | | Females (n=1036) | | |
|---|---|---|---|---|---|---|---|
| | | Frequency | Regression coefficient (β, U/L) | *P* | Frequency | Regression coefficient (β, U/L) | *P* |
| ALT | C-T | 0.444 | 6.820 | $2.74 \times 10^{-5}$ | 0.473 | 2.490 | $1.54 \times 10^{-4}$ |
| ALT | C-C | 0.045 | 4.460 | 0.255 | 0.040 | 3.100 | 0.064 |
| ALT | G-C | 0.506 | −7.710 | $2.02 \times 10^{-6}$ | 0.483 | −3.020 | $5.51 \times 10^{-6}$ |
| AST | C-T | 0.444 | 3.580 | $3.63 \times 10^{-3}$ | 0.473 | 0.741 | 0.260 |
| AST | C-C | 0.045 | 5.980 | 0.043 | 0.040 | 1.500 | 0.367 |
| AST | G-C | 0.506 | −4.840 | $8.10 \times 10^{-5}$ | 0.483 | −1.070 | 0.108 |

**Table 4**

Discrete trait association test between *PNPLA3* polymorphisms and ALT/AST levels

| cutoff | ALT and rs738409-C in males (n=496) | | | ALT and rs738409-C in females (n=1036) | | | ALT and rs2281135-T in males (n=496) | | | ALT and rs2281135-T in females (n=1036) | | | AST and rs738409-C in males (n=496) | | | AST and rs738409-C in females (n=1036) | | | AST and rs2281135-T in males (n=496) | | | AST and rs2281135-T in females (n=1036) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* | >cutoff (n) | OR (95%CI) | *P* |
| 30 | 443 | 0.926(0.620, 1.382) | 0.705 | 791 | 1.355(1.095, 1.677) | 5.21E-03 | 443 | 0.901(0.596, 1.363) | 0.622 | 791 | 1.322(1.066, 1.638) | 0.011 | 295 | 1.283(0.979, 1.681) | 0.070 | 532 | 1.083(0.907, 1.294) | 0.379 | 295 | 1.241(0.942, 1.634) | 0.125 | 532 | 1.083(0.907, 1.294) | 0.377 |
| 31 | 435 | 0.925(0.624, 1.371) | 0.697 | 717 | 1.298(1.067, 1.579) | 9.03E-03 | 435 | 0.929(0.615, 1.402) | 0.725 | 717 | 1.316(1.081, 1.602) | 6.18E-03 | 278 | 1.243(0.950, 1.627) | 0.112 | 507 | 1.018(0.852, 1.217) | 0.846 | 278 | 1.170(0.890, 1.538) | 0.261 | 507 | 1.013(0.848, 1.210) | 0.888 |
| 32 | 416 | 1.109(0.779, 1.580) | 0.565 | 659 | 1.359(1.127, 1.639) | 1.34E-03 | 416 | 1.092(0.748, 1.596) | 0.649 | 659 | 1.336(1.108, 1.612) | 2.43E-03 | 269 | 1.331(1.019, 1.740) | 0.036 | 489 | 1.022(0.855, 1.222) | 0.812 | 269 | 1.236(0.941, 1.623) | 0.127 | 489 | 1.026(0.859, 1.226) | 0.777 |
| 33 | 399 | 1.146(0.823, 1.595) | 0.421 | 605 | 1.449(1.206, 1.740) | 7.21E-05 | 399 | 1.116(0.787, 1.582) | 0.540 | 605 | 1.398(1.165, 1.678) | 3.23E-04 | 254 | 1.415(1.082, 1.851) | 0.011 | 464 | 1.030(0.860, 1.234) | 0.748 | 254 | 1.343(1.022, 1.765) | 0.034 | 464 | 1.049(0.877, 1.255) | 0.598 |
| 34 | 381 | 1.113(0.812, 1.525) | 0.507 | 546 | 1.504(1.255, 1.802) | 9.77E-06 | 381 | 1.090(0.780, 1.522) | 0.614 | 546 | 1.422(1.188, 1.703) | 1.25E-04 | 248 | 1.385(1.061, 1.809) | 0.017 | 437 | 1.074(0.896, 1.289) | 0.439 | 248 | 1.341(1.021, 1.761) | 0.035 | 437 | 1.091(0.911, 1.307) | 0.346 |
| 35 | 356 | 1.165(0.863, 1.572) | 0.319 | 491 | 1.605(1.337, 1.926) | 3.84E-07 | 356 | 1.150(0.840, 1.573) | 0.383 | 491 | 1.524(1.273, 1.826) | 4.68E-06 | 235 | 1.284(0.986, 1.672) | 0.064 | 401 | 1.035(0.861, 1.245) | 0.714 | 235 | 1.213(0.926, 1.588) | 0.160 | 401 | 1.073(0.894, 1.288) | 0.448 |
| 36 | 345 | 1.160(0.865, 1.556) | 0.321 | 436 | 1.586(1.318, 1.908) | 9.97E-07 | 345 | 1.156(0.849, 1.574) | 0.357 | 436 | 1.534(1.278, 1.840) | 4.16E-06 | 221 | 1.305(1.002, 1.700) | 0.048 | 367 | 1.074(0.889, 1.297) | 0.460 | 221 | 1.244(0.950, 1.629) | 0.112 | 367 | 1.123(0.932, 1.353) | 0.222 |
| 37 | 325 | 1.121(0.846, 1.487) | 0.427 | 390 | 1.601(1.325, 1.936) | 1.14E-06 | 325 | 1.108(0.827, 1.484) | 0.491 | 390 | 1.522(1.264, 1.832) | 9.18E-06 | 209 | 1.341(1.028, 1.749) | 0.030 | 337 | 1.107(0.914, 1.341) | 0.299 | 209 | 1.260(0.962, 1.652) | 0.093 | 337 | 1.164(0.963, 1.407) | 0.116 |
| 38 | 307 | 1.211(0.920, 1.595) | 0.173 | 356 | 1.561(1.288, 1.891) | 5.66E-06 | 307 | 1.185(0.892, 1.573) | 0.241 | 356 | 1.498(1.241, 1.808) | 2.54E-05 | 194 | 1.372(1.050, 1.794) | 0.021 | 306 | 1.086(0.893, 1.321) | 0.408 | 194 | 1.290(0.982, 1.695) | 0.067 | 306 | 1.146(0.944, 1.391) | 0.169 |
| 39 | 291 | 1.166(0.889, 1.530) | 0.267 | 316 | 1.552(1.275, 1.889) | 1.17E-05 | 291 | 1.195(0.904, 1.581) | 0.210 | 316 | 1.490(1.229, 1.807) | 4.85E-05 | 182 | 1.387(1.057, 1.819) | 0.018 | 270 | 1.098(0.898, 1.342) | 0.361 | 182 | 1.312(0.997, 1.728) | 0.053 | 270 | 1.153(0.946, 1.406) | 0.160 |
| 40 | 275 | 1.200(0.915, 1.574) | 0.187 | 283 | 1.558(1.273, 1.908) | 1.72E-05 | 275 | 1.218(0.923, 1.608) | 0.164 | 283 | 1.557(1.276, 1.900) | 1.30E-05 | 174 | 1.390(1.058, 1.826) | 0.018 | 248 | 1.132(0.920, 1.393) | 0.241 | 174 | 1.358(1.031, 1.789) | 0.029 | 248 | 1.180(0.963, 1.447) | 0.111 |
| 41 | 266 | 1.261(0.962, 1.652) | 0.093 | 253 | 1.526(1.236, 1.883) | 8.31E-05 | 266 | 1.290(0.978, 1.702) | 0.071 | 253 | 1.480(1.205, 1.817) | 1.81E-04 | 162 | 1.492(1.129, 1.972) | 4.97E-03 | 226 | 1.133(0.915, 1.403) | 0.252 | 162 | 1.451(1.096, 1.920) | 9.30E-03 | 226 | 1.186(0.961, 1.464) | 0.112 |
| 42 | 257 | 1.293(0.988, 1.692) | 0.061 | 230 | 1.487(1.196, 1.848) | 3.54E-04 | 257 | 1.301(0.988, 1.713) | 0.061 | 230 | 1.457(1.179, 1.800) | 4.95E-04 | 153 | 1.540(1.159, 2.046) | 2.94E-03 | 199 | 1.079(0.864, 1.348) | 0.505 | 153 | 1.499(1.127, 1.993) | 5.40E-03 | 199 | 1.109(0.890, 1.381) | 0.358 |
| 43 | 241 | 1.407(1.074, 1.841) | 0.013 | 206 | 1.529(1.216, 1.922) | 2.78E-04 | 241 | 1.430(1.085, 1.884) | 0.011 | 206 | 1.494(1.197, 1.864) | 3.82E-04 | 144 | 1.612(1.206, 2.156) | 1.28E-03 | 177 | 1.071(0.847, 1.355) | 0.566 | 144 | 1.542(1.154, 2.059) | 3.39E-03 | 177 | 1.075(0.854, 1.355) | 0.538 |
| 44 | 226 | 1.434(1.094, 1.879) | 8.95E-03 | 189 | 1.456(1.150, 1.843) | 1.79E-03 | 226 | 1.408(1.069, 1.853) | 0.015 | 189 | 1.411(1.124, 1.772) | 3.04E-03 | 134 | 1.491(1.106, 2.010) | 8.75E-03 | 149 | 1.156(0.898, 1.488) | 0.260 | 134 | 1.347(1.002, 1.811) | 0.049 | 149 | 1.160(0.907, 1.483) | 0.236 |
| 45 | 212 | 1.470(1.119, 1.932) | 5.63E-03 | 174 | 1.471(1.153, 1.878) | 1.91E-03 | 212 | 1.446(1.096, 1.908) | 9.03E-03 | 174 | 1.420(1.124, 1.793) | 3.27E-03 | 127 | 1.559(1.145, 2.122) | 4.84E-03 | 136 | 1.145(0.885, 1.480) | 0.304 | 127 | 1.403(1.034, 1.904) | 0.030 | 136 | 1.139(0.887, 1.464) | 0.308 |
| 46 | 197 | 1.506(1.142, 1.988) | 3.78E-03 | 162 | 1.489(1.159, 1.912) | 1.84E-03 | 197 | 1.557(1.175, 2.064) | 2.07E-03 | 162 | 1.436(1.132, 1.822) | 2.90E-03 | 115 | 1.835(1.316, 2.558) | 3.45E-04 | 125 | 1.150(0.880, 1.504) | 0.306 | 115 | 1.573(1.143, 2.164) | 5.40E-03 | 125 | 1.103(0.849, 1.434) | 0.462 |
| 47 | 183 | 1.573(1.186, 2.085) | 1.65E-03 | 147 | 1.613(1.235, 2.107) | 4.52E-04 | 183 | 1.633(1.227, 2.175) | 7.86E-04 | 147 | 1.480(1.156, 1.895) | 1.88E-03 | 103 | 1.674(1.183, 2.369) | 3.61E-03 | 110 | 1.241(0.931, 1.652) | 0.141 | 103 | 1.479(1.066, 2.051) | 0.019 | 110 | 1.176(0.890, 1.553) | 0.254 |
| 48 | 167 | 1.451(1.090, 1.931) | 0.011 | 131 | 1.743(1.300, 2.336) | 2.04E-04 | 167 | 1.498(1.120, 2.004) | 6.41E-03 | 131 | 1.594(1.219, 2.085) | 6.66E-04 | 97 | 1.644(1.150, 2.351) | 6.47E-03 | 102 | 1.277(0.954, 1.711) | 0.100 | 97 | 1.464(1.042, 2.055) | 0.028 | 102 | 1.203(0.907, 1.596) | 0.200 |
| 49 | 150 | 1.652(1.224, 2.230) | 1.03E-03 | 120 | 1.810(1.331, 2.462) | 1.56E-04 | 150 | 1.697(1.255, 2.296) | 5.94E-04 | 120 | 1.662(1.254, 2.202) | 4.08E-04 | 90 | 1.627(1.127, 2.349) | 9.44E-03 | 93 | 1.311(0.962, 1.786) | 0.086 | 90 | 1.468(1.034, 2.085) | 0.032 | 93 | 1.230(0.911, 1.659) | 0.177 |
| 50 | 141 | 1.635(1.209, 2.210) | 1.40E-03 | 110 | 1.739(1.275, 2.373) | 4.76E-04 | 141 | 1.665(1.229, 2.254) | 9.87E-04 | 110 | 1.587(1.193, 2.112) | 1.51E-03 | 83 | 1.646(1.130, 2.398) | 9.46E-03 | 78 | 1.350(0.958, 1.904) | 0.087 | 83 | 1.463(1.024, 2.090) | 0.037 | 78 | 1.232(0.888, 1.708) | 0.211 |
| 51 | 136 | 1.710(1.259, 2.323) | 5.93E-04 | 105 | 1.776(1.291, 2.442) | 4.15E-04 | 136 | 1.727(1.271, 2.346) | 4.71E-04 | 105 | 1.648(1.227, 2.213) | 9.02E-04 | 78 | 1.832(1.231, 2.726) | 2.85E-03 | 72 | 1.448(1.010, 2.076) | 0.044 | 78 | 1.579(1.093, 2.281) | 0.015 | 72 | 1.335(0.948, 1.879) | 0.098 |
| 52 | 129 | 1.719(1.254, 2.356) | 7.63E-04 | 98 | 1.813(1.306, 2.516) | 3.79E-04 | 129 | 1.700(1.242, 2.328) | 9.31E-04 | 98 | 1.661(1.229, 2.245) | 9.57E-04 | 69 | 1.753(1.173, 2.620) | 6.16E-03 | 66 | 1.423(0.990, 2.046) | 0.057 | 69 | 1.557(1.065, 2.277) | 0.022 | 66 | 1.340(0.951, 1.887) | 0.094 |
| 53 | 124 | 1.778(1.293, 2.445) | 4.03E-04 | 92 | 1.784(1.270, 2.506) | 8.48E-04 | 124 | 1.752(1.276, 2.404) | 5.19E-04 | 92 | 1.599(1.173, 2.182) | 3.03E-03 | 67 | 1.704(1.137, 2.552) | 9.77E-03 | 60 | 1.429(0.979, 2.085) | 0.064 | 67 | 1.502(1.024, 2.204) | 0.038 | 60 | 1.322(0.927, 1.885) | 0.124 |
| 54 | 116 | 1.815(1.316, 2.503) | 2.81E-04 | 87 | 1.824(1.283, 2.593) | 8.06E-04 | 116 | 1.777(1.293, 2.442) | 3.99E-04 | 87 | 1.607(1.170, 2.208) | 3.42E-03 | 60 | 2.012(1.276, 3.172) | 2.62E-03 | 54 | 1.521(1.011, 2.287) | 0.044 | 60 | 1.922(1.248, 2.959) | 3.03E-03 | 54 | 1.396(0.962, 2.026) | 0.079 |
| 55 | 109 | 1.816(1.308, 2.520) | 3.64E-04 | 81 | 1.682(1.177, 2.404) | 4.30E-03 | 109 | 1.807(1.303, 2.506) | 3.87E-04 | 81 | 1.516(1.097, 2.094) | 0.012 | 55 | 2.413(1.446, 4.028) | 7.52E-04 | 51 | 1.452(0.960, 2.195) | 0.077 | 55 | 2.208(1.386, 3.520) | 8.66E-04 | 51 | 1.322(0.904, 1.933) | 0.151 |
| 56 | 107 | 1.949(1.390, 2.732) | 1.08E-04 | 76 | 1.613(1.125, 2.314) | 9.36E-03 | 107 | 1.922(1.376, 2.684) | 1.26E-04 | 76 | 1.445(1.041, 2.006) | 0.028 | 50 | 2.649(1.515, 4.633) | 6.35E-04 | 49 | 1.399(0.922, 2.122) | 0.115 | 50 | 2.421(1.483, 3.953) | 4.10E-04 | 49 | 1.268(0.863, 1.863) | 0.227 |
| 57 | 102 | 1.900(1.355, 2.663) | 1.97E-04 | 71 | 1.544(1.074, 2.222) | 0.019 | 102 | 1.865(1.335, 2.605) | 2.58E-04 | 71 | 1.404(1.009, 1.953) | 0.044 | 48 | 2.646(1.513, 4.627) | 6.46E-04 | 44 | 1.446(0.934, 2.238) | 0.098 | 48 | 2.418(1.481, 3.948) | 4.18E-04 | 44 | 1.385(0.925, 2.072) | 0.114 |
| 58 | 98 | 2.059(1.450, 2.924) | 5.44E-05 | 66 | 1.607(1.102, 2.344) | 0.014 | 98 | 1.996(1.415, 2.814) | 8.11E-05 | 66 | 1.437(1.024, 2.017) | 0.036 | 45 | 2.672(1.527, 4.675) | 5.78E-04 | 42 | 1.501(0.948, 2.377) | 0.084 | 45 | 2.443(1.495, 3.993) | 3.65E-04 | 42 | 1.408(0.927, 2.140) | 0.109 |
| 59 | 93 | 2.162(1.494, 3.130) | 4.36E-05 | 59 | 1.659(1.119, 2.461) | 0.012 | 93 | 2.038(1.424, 2.916) | 9.81E-05 | 59 | 1.445(1.019, 2.050) | 0.039 | 40 | 2.488(1.415, 4.373) | 1.55E-03 | 40 | 1.630(1.004, 2.646) | 0.048 | 40 | 2.480(1.461, 4.209) | 7.63E-04 | 40 | 1.593(1.019, 2.491) | 0.041 |
| 60 | 88 | 2.132(1.454, 3.126) | 1.06E-04 | 55 | 1.795(1.162, 2.772) | 8.32E-03 | 88 | 1.960(1.355, 2.835) | 3.56E-04 | 55 | 1.516(1.049, 2.192) | 0.027 | 39 | 2.399(1.362, 4.228) | 2.46E-03 | 36 | 1.449(0.881, 2.384) | 0.144 | 39 | 2.473(1.457, 4.198) | 7.94E-04 | 36 | 1.399(0.880, 2.225) | 0.156 |

**Table 5**

Quantitative trait association test between *PNPLA3* polymorphisms and metabolic criteria

| Trait | SNP (reference allele) | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| | | Regression coefficient (β) | Standard error (SE) | *P* | Regression coefficient (β) | Standard error (SE) | *P* |
| BMI | rs738409 (C) | 0.263 | 0.401 | 0.512 | 0.030 | 0.331 | 0.927 |
| BMI | rs2281135 (T) | 0.165 | 0.411 | 0.689 | −0.124 | 0.330 | 0.708 |
| HOMA-IR | rs738409 (C) | 0.139 | 0.286 | 0.629 | −0.241 | 0.172 | 0.162 |
| HOMA-IR | rs2281135 (T) | 0.221 | 0.293 | 0.452 | −0.331 | 0.172 | 0.054 |
| Adiponectin * | rs738409 (C) | −1.082 (pg/ml) | 1.561 | 0.493 | 1.213 (pg/ml) | 1.484 | 0.415 |
| adiponectin * | rs2281135 (T) | −1.893 (pg/ml) | 1.511 | 0.219 | 0.769 (pg/ml) | 1.526 | 0.615 |
| Leptin * | rs738409 (C) | −3009 (ng/ml) | 2768 | 0.285 | 2284 (ng/ml) | 4304 | 0.597 |
| Leptin * | rs2281135 (T) | −446 (ng/ml) | 2767 | 0.873 | 2144 (ng/ml) | 4428 | 0.629 |
| Log(leptin/adiponectin) * | rs738409 (C) | −0.232 | 0.186 | 0.220 | 0.029 | 0.061 | 0.635 |
| Log(leptin/adiponectin) * | rs2281135 (T) | 0.035 | 0.181 | 0.848 | 0.051 | 0.063 | 0.418 |

* The quantitative trait association test of adiponectin, leptin, and Log(leptin/adiponectin) was based on the measurement of adiponectin and leptin at protein levels in 153 individuals randomly selected from the subjects in this study[21].