# Association of *HSD17B13* and *PNPLA3* With Liver Enzymes and Fibrosis in Hispanic/Latino Individuals of Diverse Genetic Ancestries

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**BACKGROUND & AIMS:** **Genetic variants affecting liver disease risk vary among racial and ethnic groups. Hispanics/Latinos in the United States have a high prevalence of *PNPLA3* I148M, which increases liver disease risk, and a low prevalence of *HSD17B13* predicted loss-of-function (pLoF) variants, which reduce risk. Less is known about the prevalence of liver disease–associated variants among Hispanic/Latino subpopulations defined by country of origin and genetic ancestry. We evaluated the prevalence of *HSD17B13* pLoF variants and *PNPLA3* I148M, and their associations with quantitative liver phenotypes in Hispanic/Latino participants from an electronic health record–linked biobank in New York City.**

**METHODS:** **This study included 8739 adult Hispanic/Latino participants of the Bio*Me* biobank with genotyping and exome sequencing data. We estimated the prevalence of Hispanic/Latino individuals harboring *HSD17B13* and *PNPLA3* variants, stratified by genetic ancestry, and performed association analyses between variants and liver enzymes and Fibrosis-4 (FIB-4) scores.**

**RESULTS:** **Individuals with ancestry from Ecuador and Mexico had the lowest frequency of *HSD17B13* pLoF variants (10%/7%) and the highest frequency of *PNPLA3* I148M (54%/65%). These ancestry groups had the highest outpatient alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and the largest proportion of individuals with a FIB-4 score greater than 2.67. *HSD17B13* pLoF variants were associated with reduced ALT level ($P = .002$), AST level ($P < .001$), and FIB-4 score ($P = .045$). *PNPLA3* I148M was associated with increased ALT level, AST level, and FIB-4 score ($P < .001$ for all). *HSD17B13* pLoF variants mitigated the increase in ALT conferred by *PNPLA3* I148M ($P = .006$).**

**CONCLUSIONS:** **Variation in *HSD17B13* and *PNPLA3* variants across genetic ancestry groups may contribute to differential risk for liver fibrosis among Hispanic/Latino individuals.**

*Keywords:* Biobank; Electronic Health Records; FIB-4 Score; Genetic Risk; Hispanic/Latino; *HSD17B13*; Liver Fibrosis; NAFLD; *PNPLA3*.

Chronic liver disease (CLD) is a major cause of morbidity and mortality among Hispanics/Latinos (also includes Latina, LatinX, Latine, and others of Latin origin) in the United States.[1] Irrespective of the etiology, Hispanics/Latinos have a higher incidence and more aggressive pattern of CLD than White/European Americans.[1–4] Variations in behavioral patterns and health care access have been hypothesized as

***Abbreviations used in this paper:*** **ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; BMI, body mass index; CLD, chronic liver disease; EHR, electronic health record; FIB-4, Fibrosis-4; ICD-9, International Classification of Diseases, 9th revision; ICD-10, International Classification of Diseases, 10th revision; MAF, minor allele frequency; NAFLD, nonalcoholic fatty liver disease; PC, principal component of ancestry; pLoF, predicted loss-of-function.**

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explanations, but genetic risk factors also are likely to play a role.[5]

The common variant rs738409:G (I148M) in *PNPLA3*, encoding patatin-like phospholipase domain-containing protein 3, is the most well-established variant associated with an increased risk of CLD and fibrosis, and is more prevalent in Hispanics/Latinos.[6,7] More recently, a splice variant in *HSD17B13* (rs72613567:TA), encoding a hepatic lipid droplet protein, hydroxysteroid 17-$\beta$ dehydrogenase 13, has been associated with reduced risk of nonalcoholic fatty liver disease (NAFLD), alcohol-associated liver disease, hepatic fibrosis, and liver-related mortality.[8–14] Few studies have examined the impact of *HSD17B13* rs72613567:TA or other *HSD17B13* predicted loss-of-function (pLoF) variants on liver disease risk in Hispanics/Latinos.[14,15]

Here, we evaluated the prevalence and clinical impact of *HSD17B13* and *PNPLA3* in a diverse patient population in New York City. We identified liver disease–associated variants in *HSD17B13* and *PNPLA3* in self-reported Hispanics/Latinos, evaluated their prevalence in subpopulations defined by country of origin and genetic ancestry, and assessed for associations with quantitative liver phenotypes, including liver enzymes and Fibrosis-4 (FIB-4) score, using electronic health record (EHR) data.

### What You Need to Know

#### Background

Hispanic/Latino individuals in the United States have a high prevalence of liver disease. We examined genetic variants impacting liver disease risk among Hispanic/Latino subpopulations defined by country of origin and genetic ancestry.

#### Findings

Individuals with ancestry from Ecuador or Mexico had low frequencies of *HSD17B13* loss-of-function variants (associated with reduced liver enzyme levels and fibrosis) and high frequencies of *PNPLA3* I148M (associated with increased liver enzyme levels and fibrosis).

#### Implications for patient care

Genetic variation across ancestry groups may contribute to differential risk for liver disease among Hispanic/Latino individuals. Better understanding of genetic risk may help to identify patients for earlier screening and interventions.

## Materials and Methods

### *Study Population*

The Bio*Me* Biobank is an EHR-linked biobank of approximately 60,000 participants from the Mount Sinai Health System in New York City. Recruitment into Bio*Me* has been ongoing since 2007 and occurs predominantly through ambulatory care practices across the Mount Sinai Health System. This study included 8739 consented adult Hispanic/Latino participants (age, $\geq$18 y) of Bio*Me*, enrolled between 2007 and 2015, with both genotype array and exome sequence data available.[16,17] The study was approved by the Icahn School of Medicine at Mount Sinai's Institutional Review Board (protocol number 07–0529) and complies with Health Information Privacy and Portability Act regulations.

### *Identification of Liver-Disease Associated Variants in* HSD17B13 *and* PNPLA3

Exome sequencing and genotyping on the Illumina Global Screening Array were performed by the Regeneron Genetics Center as described previously.[18] Samples were filtered by removal of low-quality samples (low-coverage, contaminated, genotype-exome discordant, and duplicate samples) as well as sites with excessive missingness and allele imbalance. Details of post hoc filtering are described elsewhere.[16,19] *PNPLA3* rs738409 (p.Ile148Met or I148M) variant status was identified in all samples that passed quality control. *HSD17B13* pLoF variants were identified using Ensembl Variant- Effect Predictor and included frameshift, splice donor, or stop gained variants. All variants were tested for Hardy-Weinberg equilibrium using the chi-squared test before analysis. We aggregated all *HSD17B13* pLoF variants to estimate their overall prevalence. For all analyses, we excluded second-degree relatives and closer, as previously described.[16]

### *Race/Ethnicity and Genetic Ancestry Designations*

Self-reported race and ethnicity categories were derived from a multiple-choice survey administered to participants at the time of enrollment into Bio*Me*. Genetic ancestry in the form of identity-by-descent communities was available for a subset of participants; details are described by Belbin et al.[17] Country-of-origin information was used if the participant, both parents, or 3 or more grandparents were born in a specific country outside the United States. Using a combination of country of origin and genetic ancestry, 6 communities were determined to have recent ancestry from Puerto Rico, the Dominican Republic, Ecuador, Colombia, Mexico, and other Central and South American communities (referred to as *genetic ancestry groups*).

### *Electronic Health Record–Based Liver Enzyme and Fibrosis Phenotypes*

We extracted age, sex, height, weight, and outpatient laboratory values for aspartate aminotransferase (AST),

alanine aminotransferase (ALT), and platelets from the EHR. For participants with more than 1 laboratory measure, median values were used. For association analyses, we excluded individuals with any International Classification of Diseases, 9th or 10th revisions (ICD-9 or ICD-10) diagnosis code for chronic hepatitis B or C infection (Supplementary Table 1). We performed a sensitivity analysis excluding individuals with ICD-9/ICD-10 codes for alcohol use disorder (AUD) or other etiologies of CLD, including alcohol-associated liver disease (Supplementary Table 1).[20]

The FIB-4 score was defined as follows: $FIB4 = (age\ [years] \times AST\ [U/L]) / (platelet\ count\ (10^9/L) \times \sqrt{ALT\ (U/L)})$, and repeated measurements could help identify those at risk for severe liver disease.[21,22] We calculated the first available and most recent FIB-4 scores, in addition to body mass index (BMI) closest in time to these scores. We performed association analyses with FIB-4 scores in individuals aged 35 years or older, given the low likelihood of advanced fibrosis in younger individuals.[21] We performed sensitivity analyses including participants of all ages and after adjusting for type 2 diabetes. We used a FIB-4 threshold of greater than 2.67 to define advanced fibrosis because this has been shown to be a predictor of mortality in NAFLD.[23]

### Statistical Analysis

Continuous variables are presented as means (SD) if normally distributed or as the median (interquartile range) if skewed. Categoric variables are presented as number (percentage). Samples with missing data for any covariates were removed from downstream analyses. Values for BMI, ALT, AST, and FIB-4 scores were natural log-transformed before performing linear regression to account for skewed distributions.

To compare liver enzyme levels and FIB-4 scores across genetic ancestry groups, the multinominal propensity scores function from Toolkit for Weighting and Analysis of Nonequivalent Groups was used to estimate the propensity score weights after adjusting for sex, age at laboratory test date, and BMI.[24]

We performed linear regression to evaluate associations between genetic variants (*HSD17B13* pLoF variants, *PNPLA3* I148M, and both *HSD17B13* pLoF and *PNPLA3* I148M variants as a multiplicative interaction term) and liver enzyme values, adjusting for age, sex, and BMI. For association analyses with FIB-4 score, age was not included as a covariate because it was included in generation of the score, but we performed an analysis stratifying participants into age ranges (35–50 years, 51–65 years, and >65 years). We adjusted for the first 5 principal components of ancestry (PCs) in a secondary analysis. *T* tests and chi-squared tests were used to compare means and proportions between groups, respectively. Kruskal–Wallis tests were used for comparisons between multiple groups. The change in FIB-4 score/year was the absolute difference in the first available and most recent FIB-4 score for an individual, divided by the number of years between the scores.

Association analyses were performed using R (2021, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org). All other analyses were performed using StataCorp (2021, *Stata Statistical Software: Release 17*; StataCorp, LLC, College Station, TX). The Strengthening the Reporting of Observational Studies in Epidemiology cross-sectional reporting guidelines were used.

## Results

### Study Population

This study included 8739 adult, unrelated, self-reported Hispanic/Latino participants from the Bio*Me* Biobank with available genotyping and exome sequencing data (Table 1 and Supplementary Tables 2–4). Participants had a mean of 7.8 (SD, 3.6) years of EHR data. The greatest number had genetic ancestry from Puerto Rico (n = 4819) or the Dominican Republic (n = 1797). Figure 1 shows the selection of participants for downstream analyses. After excluding participants with missing data or with laboratory values or BMI greater than 4 SDs from the mean, the number of participants included in ALT, AST, and FIB-4 score analyses were 4910, 4856, and 4150, respectively (Figure 1).

ALT and AST levels were higher in Ecuadorian and Mexican groups than in Colombian, Dominican, and Puerto Rican groups. The most recent FIB-4 scores were significantly higher in participants with ancestry from Ecuador compared with those from Colombia, the Dominican Republic, other Central and South American communities, and Puerto Rico. We found a higher proportion of participants with a FIB-4 score greater than 2.67 among individuals with ancestry from Ecuador compared with Puerto Rico (Table 1).

### *Prevalence of* HSD17B13 *and* PNPLA3 *Variants*

We identified 9 pLoF variants in *HSD17B13* in Bio*Me* (Supplementary Table 5). In unrelated Hispanics/Latinos (n = 8739), the overall minor allele frequency (MAF) of all *HSD17B13* pLoF variants in aggregate was 20.4%. The most common pLoF variant in *HSD17B13* was rs72613567 (MAF, 14.9%), followed by rs143404524 (c.573delC; MAF, 5.9%) (Supplementary Table 5). Hispanics/Latinos had a lower frequency of *HSD17B13* pLoF variants than most other self-reported population groups in Bio*Me* (Supplementary Figure 1). Within the Hispanic/Latino population group, individuals with genetic ancestry from the Dominican Republic or Puerto Rico had the highest frequency of *HSD17B13* pLoF variants: 22.4% (95% CI, 20.5–24.4) and 22.1% (95% CI, 20.9–23.3), respectively. Individuals with ancestry from Ecuador or Mexico had the lowest frequency: 9.7% (95%

**Table 1.** Demographics and Clinical Characteristics of Unrelated, Adult Hispanics/Latinos From the Bio*Me* Biobank, Overall and Within the 6 Largest Genetic Ancestry Groups

| | | Genetic ancestry group, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristic | Unrelated, self-reported Hispanics/Latinos (n = 8739) | Colombia, 138 (1.6) | Dominican Republic, 1797 (20.6) | Ecuador, 406 (4.6) | Mexico, 219 (2.5) | Other Central and South American communities, 775 (8.9) | Puerto Rico, 4819 (55.1) | Other genetic ancestry, 585 (6.7) |
| Age at enrollment, *y*, mean (SD) (n = 8739)[a] | 51.8 (16.4) | 51.8 (14.5) | 53.1 (17.2) | 52.9 (16.2) | 40.4 (11.7) | 50.9 (16.8) | 52.3 (16.0) | 48.9 (16.7) |
| Age at enrollment, *y*, n (%) (n = 8739)[a] | | | | | | | | |
| <35 | 876 (10.0) | 16 (11.6) | 197 (11.0) | 32 (7.9) | 32 (15.0) | 86 (11.1) | 424 (8.8) | 152 (26.0) |
| 35–50 | 1583 (18.1) | 16 (11.6) | 276 (15.4) | 69 (17.0) | 62 (28.2) | 159 (20.5) | 895 (18.6) | 146 (24.9) |
| 51–65 | 2346 (26.9) | 48 (34.8) | 368 (20.5) | 107 (26.4) | 36 (16.4) | 186 (24.0) | 1462 (30.3) | 176 (30.1) |
| >65 | 3934 (45.0) | 58 (42.0) | 956 (53.2) | 198 (48.8) | 89 (40.4) | 344 (44.4) | 2038 (42.3) | 111 (19.0) |
| Age at most recent laboratory tests, *y*, n (%) (n = 6935)[a] | 55.3 (17.1) | 52.7 (14.7) | 54.2 (17.3) | 56.7 (16.1) | 43.9 (12.7) | 54.1 (17.0) | 56.3 (17.1) | 52.4 (17.2) |
| Age at most recent laboratory tests, *y*, n (%) (n = 6935)[a] | | | | | | | | |
| <35 | 986 (14.2) | 16 (17.2) | 192 (17.3) | 31 (11.0) | 31 (23.7) | 82 (15.6) | 416 (12.6) | 89 (19.8) |
| 35–50 | 1646 (23.7) | 16 (17.2) | 261 (23.6) | 66 (23.3) | 61 (46.6) | 140 (26.7) | 773 (23.5) | 106 (23.6) |
| 51–65 | 2200 (31.7) | 44 (47.3) | 319 (28.8) | 99 (35.0) | 33 (25.2) | 156 (29.7) | 1071 (32.5) | 139 (31.0) |
| >65 | 2103 (30.2) | 17 (18.3) | 336 (30.3) | 87 (30.7) | 6 (4.6) | 147 (28.0) | 1035 (31.4) | 115 (25.6) |
| Female sex, n (%) (n = 8739)[a] | 5431 (62.1) | 78 (56.5) | 1200 (66.8) | 238 (58.6) | 127 (58.0) | 434 (56.1) | 2983 (61.9) | 369 (63.1) |
| Education level of high school or above, n (%) (n = 2663)[a] | 2082 (78.2) | 38 (82.6) | 409 (68.7) | 113 (75.3) | 60 (50) | 216 (86.8) | 1094 (82.3) | 152 (87.4) |
| BMI, $kg/m^2$, median (IQR) (n = 5881)[a] | 28.5 (24.9–33.1) | 26.2 (23.6–30.4) | 28.0 (24.8–31.8) | 28.4 (25.2–32.1) | 29.3 (26.2–32.9) | 27.5 (24.4–31.9) | 29.0 (25.1–33.7) | 28.3 (24.9–33.5) |
| Obesity, n (%) (n = 5881)[a] | 2395 (40.7) | 20 (25.3) | 365 (35.4) | 106 (39.4) | 46 (40.4) | 166 (33.1) | 1538 (44.0) | 154 (39.8) |

**Table 1.** Continued

| Characteristic | Unrelated, self-reported Hispanics/Latinos (n = 8739) | Genetic ancestry group, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Colombia, 138 (1.6) | Dominican Republic, 1797 (20.6) | Ecuador, 406 (4.6) | Mexico, 219 (2.5) | Other Central and South American communities, 775 (8.9) | Puerto Rico, 4819 (55.1) | Other genetic ancestry, 585 (6.7) |
| Hypertension, n (%) (n = 8739)[a] | 4990 (57.1) | 53 (38.4) | 1079 (60.0) | 208 (51.2) | 61 (27.9) | 360 (46.5) | 2911 (60.4) | 318 (54.3) |
| Type 2 diabetes, n (%) (n = 7788)[a] | 2629 (33.8) | 21 (16.5) | 500 (31.1) | 94 (26.0) | 50 (24.5) | 179 (25.0) | 1647 (38.9) | 138 (26.0) |
| Median outpatient ALT level, *U/L*, weighted mean (95% CI) (n) | 24.9 (24.1–25.8) (n = 6237) | 23.2 (20.5–25.9) (n = 98) | 23.4 (22.3–24.4) (n = 1205) | 28.1 (26.0–30.2) (n = 303)[b] | 31.3 (26.3–36.3) (n = 151)[b] | 25.3 (23.5–27.2) (n = 558) | 22.9 (22.2–23.6) (n = 3489) | 21.5 (20.2–22.8) (n = 433) |
| Median outpatient AST level, *U/L*, weighted mean (95% CI) (n) | 24.8 (24.1–25.4) (n = 6053) | 22.4 (20.7–24.1) (n = 95) | 24.0 (23.1–25.0) (n = 1126) | 26.5 (25.1–27.8) (n = 292)[c] | 29.6 (26.0–33.3) (n = 146)[c] | 25.2 (24.0–26.4) (n = 542) | 23.1 (22.5–23.7) (n = 3431) | 23.2 (21.5–24.9) (n = 421) |
| Most recent FIB-4 score, weighted mean (95% CI) (n) | 1.73 (1.55–1.91) (n = 4960) | 1.53 (1.20–1.85) (n = 77) | 1.52 (1.43–1.61) (n = 907) | 2.01 (1.64–2.38) (n = 252)[b] | 2.47 (1.11–3.83) (n = 99) | 1.69 (1.48–1.89) (n = 443) | 1.55 (1.44–1.65) (n = 2865) | 1.52 (1.33–1.72) (n = 317) |
| Most recent FIB-4 score >2.67, weighted prevalence (95% CI) (n) | 10.10 (8.27–11.93) (n = 4960) | 10.20 (1.53–18.87) (n = 77) | 8.33 (6.43–10.24) (n = 907) | 12.16 (8.04–16.29) (n = 252)[d] | 15.63 (6.16–25.09) (n = 99) | 11.20 (8.18–14.22) (n = 443) | 7.15 (6.22–8.08) (n = 2865) | 7.32 (4.17–10.47) (n = 317) |
| Time between FIB-4 scores, *y*, weighted mean (SD) (n)[a] | 7.4 (4.4) (n = 3852) | 5.9 (3.8) (n = 57) | 6.8 (4.4) (n = 607) | 7.1 (4.1) (n = 196) | 6.8 (4.3) (n = 74) | 6.3 (3.9) (n = 336) | 7.8 (4.6) (n = 2323) | 6.7 (4.0) (n = 259) |
| Change in FIB-4/y, weighted mean (95% CI) (n) | 0.07 (0.04–0.09) (n = 3852) | 0.01 (-0.06 to 0.08) (n = 57) | 0.05 (0.02–0.09) (n = 607) | 0.07 (-0.01 to 0.16) (n = 196) | 0.16 (-0.04 to 0.36) (n = 74) | 0.09 (0.03–0.16) (n = 336) | 0.05 (0.03–0.08) (n = 2323) | 0.05 (0.02–0.08) (n = 259) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 score; IQR, interquartile range.
[a]$P < .05$ with Kruskal–Wallis equality-of-populations rank test between genetic ancestry groups.
[b]Significantly higher than Colombia, Dominican Republic, Other Central and South American communities, and Puerto Rico.
[c]Significantly higher than Colombia, Dominican Republic, and Puerto Rico.
[d]Significantly higher than Puerto Rico.

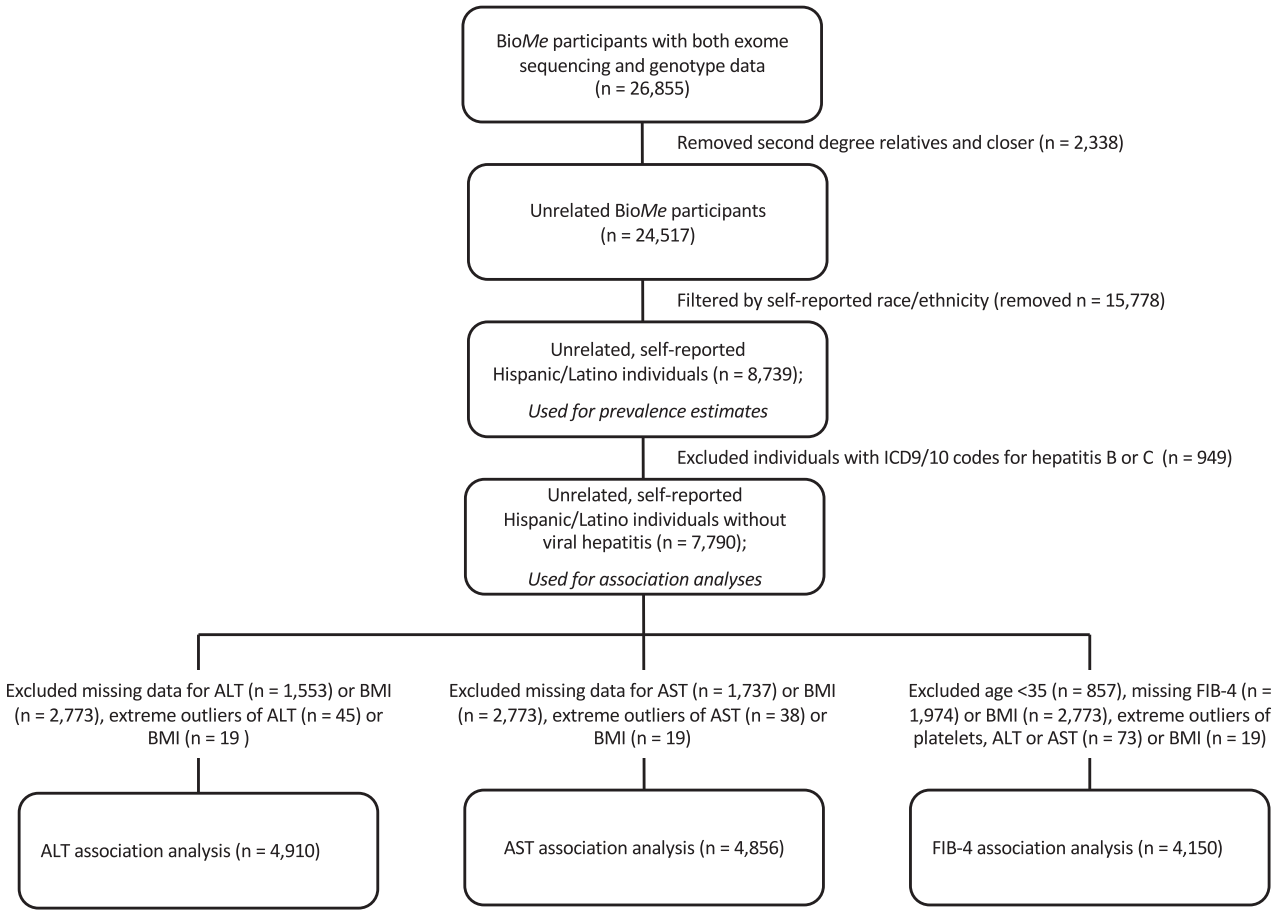


**Figure 1.** Flow diagram illustrating the inclusion and exclusion of Bio*Me* participants for association analyses. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 score; ICD-9/-10, International Classification of Diseases, 9th/10th revision; MAF, minor allele frequency.

CI, 6.8–12.6) and 6.8% (95% CI, 3.5–10.2), respectively (Figure 2).

The overall MAF of *PNPLA3* I148M in Hispanics/Latinos was 33.3%, with the highest frequency in individuals with genetic ancestry from Mexico (64.6%; 95% CI, 58.3–71.0), Ecuador (54.4%; 95% CI, 49.6–59.3), or Colombia (46.5%; 95% CI, 38.2–54.9), and the lowest frequency in those from Puerto Rico (32.1%; 95% CI, 30.7–33.4) or the Dominican Republic (27.0%; 95% CI, 25.0–29.1) (Figure 2).

### Association With Liver Enzyme Levels

Results for association analyses are presented as $\beta$ coefficient ($\pm$SE). *HSD17B13* pLoF variants were associated with reduced ALT (-0.08 [0.03]; $P = .002$) and AST (-0.10 [0.02]; $P < .001$) level, adjusting for age, sex, and BMI. Associations remained significant for AST level in participants with ancestry from Colombia or Puerto Rico (Supplementary Table 6). In a sensitivity analysis with additional adjustment for PCs, associations remained significant for both ALT (-0.06 [0.03]; $P = .03$) and AST (-0.08 [0.03]; $P = .002$) levels.

*PNPLA3* I148M was associated with increased ALT (0.16 [0.02]; $P < .001$) and AST (0.16 [0.02]; $P < .001$) levels, adjusting for age, sex, and BMI. Associations remained significant in participants with genetic ancestry from Ecuador or Puerto Rico (Supplementary Table 7). In a sensitivity analysis adjusting for PCs, associations remained significant for both ALT (0.12 [0.02]; $P < .001$) and AST (0.14 [0.02]; $P < .001$) level. The presence of any *HSD17B13* pLoF variant partially mitigated the increase in ALT level (-0.11 [0.04]; $P = .006$) conferred by *PNPLA3* I148M in a dose-dependent manner (Figure 3*A*), but the interaction term was not significant for AST level (-0.05 [0.18]; $P = .18$) (Figure 3*B* and Supplementary Table 8). Similar association results were observed in sensitivity analyses excluding individuals with ICD-9/ICD-10 codes for AUD or etiologies of non-viral CLD other than NAFLD (n = 542) (Supplementary Tables 9–11).

### Association With Most Recent Fibrosis-4 Score

In individuals aged 35 years or older, *HSD17B13* pLoF variants were associated with a lower FIB-4 score, adjusting for sex and BMI (-0.05 [0.03]; $P = .045$). This association remained significant in individuals with genetic ancestry from Ecuador or Puerto Rico (Supplementary Table 6), after adjusting for PCs (-0.06 [0.03]; $P = .02$),

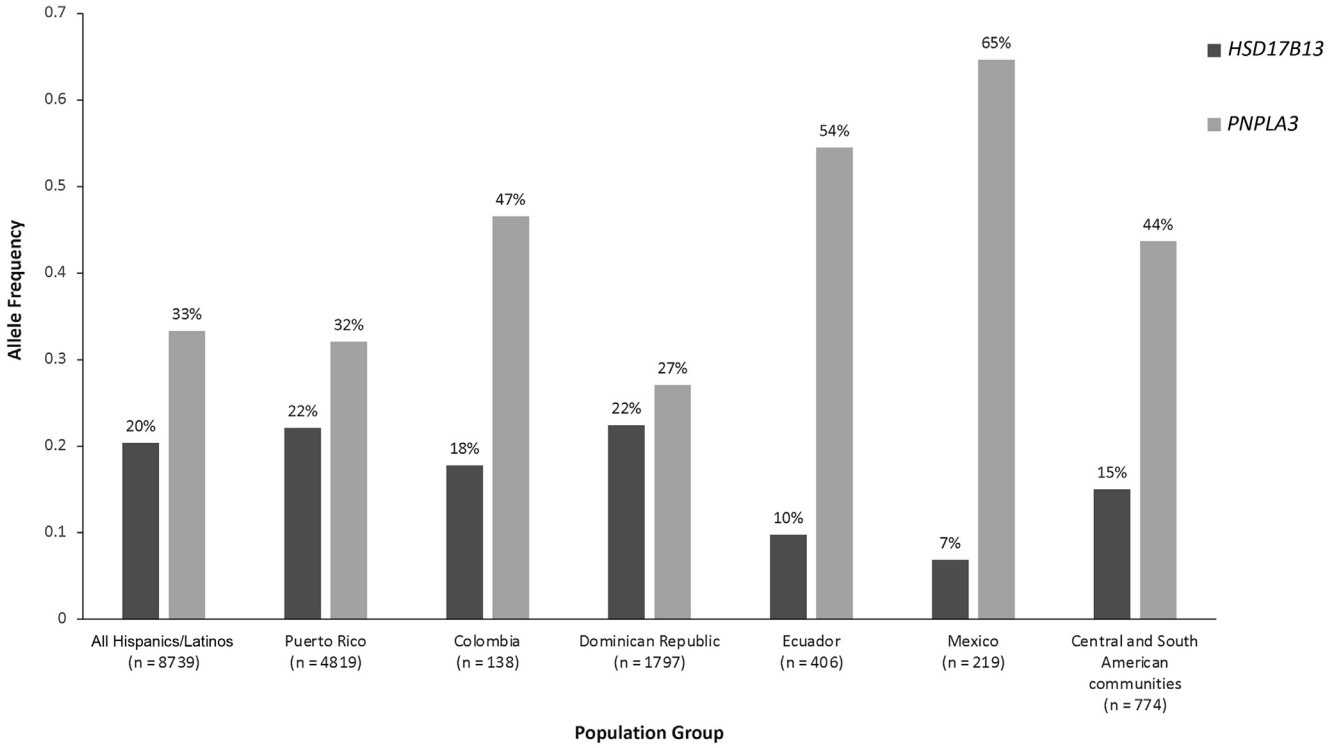


**Figure 2.** Minor allele frequency of all *HSD17B13* predicted loss-of-function variants and *PNPLA3* I148M in Hispanics/Latinos, and across genetic ancestry groups.

and in individuals older than 65 years (Supplementary Table 12). *HSD17B13* pLoF variants were not associated with advanced fibrosis or with change in FIB-4 score over time (Supplementary Table 6).

*PNPLA3* I148M was associated with a higher FIB-4 score (0.08 [0.02]; $P < .001$). This association remained significant in individuals with genetic ancestry from Ecuador or Puerto Rico (Supplementary Table 7), after adjusting for PCs (0.09 [0.02]; $P < .001$), and in individuals aged 51 to 65 years or older than 65 years (Supplementary Table 12). *PNPLA3* I148M also was associated with increased odds of advanced fibrosis (odds ratio, 1.35; 95% CI, 1.15–1.59), but not with change in FIB-4 score over time (Supplementary Table 7). Interaction analyses between *PNPLA3* and *HSD17B13* did not reveal any significant associations with FIB-4 score, FIB-4 greater than 2.67, or change in FIB-4 score over time (Figure 4 and Supplementary Table 8).

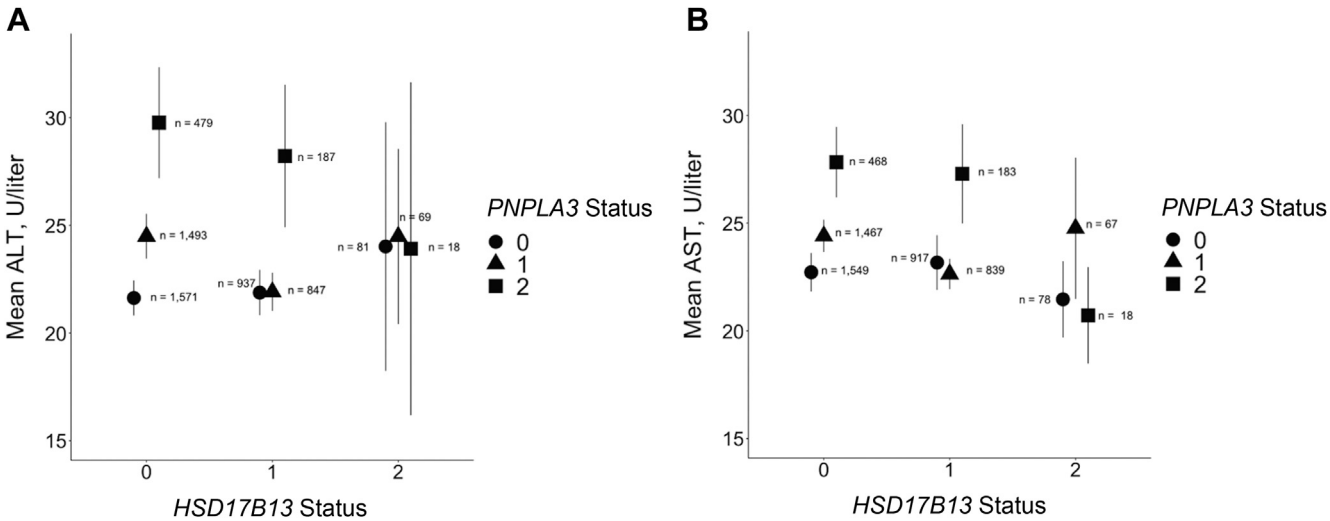


**Figure 3.** Association of *HSD17B13* pLoF variants with (*A*) alanine aminotransferase (ALT) and (*B*) aspartate aminotransferase (AST) levels in individuals with each *PNPLA3* rs738409 (I148M) genotype. *HSD17B13* pLoF genotypes on the x axis indicate reference allele homozygotes, heterozygotes, and alternate allele homozygotes (0, 1, and 2 respectively). *PNPLA3* I148M genotypes are depicted by various shapes. The *P* values for interaction between *HSD17B13* and *PNPLA3* I148M in association analyses of levels of ALT and AST were $P = .006$ and $P = .18$, respectively, with adjustment for age and sex. *Bars* indicate 95% CIs; *Circle* indicates *PNPLA3* I148M reference allele homozygotes; *Triangle* indicates *PNPLA3* I148M heterozygotes; *Square* indicates *PNPLA3* I148M alternate allele homozygotes.

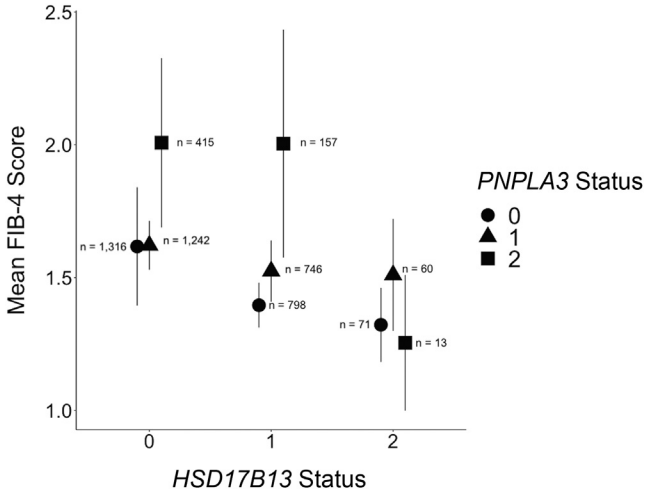


**Figure 4.** Association of *HSD17B13* predicted loss-of-function (pLoF) variants with Fibrosis-4 (FIB-4) score in persons with each *PNPLA3* rs738409 (I148M) genotype. *HSD17B13* pLoF genotypes on the x axis indicate reference allele homozygotes, heterozygotes, and alternate allele homozygotes (0, 1, and 2 respectively). *PNPLA3* I148M genotypes are depicted by various shapes. The *P* value for interaction between *HSD17B13* and *PNPLA3* I148M in association analysis of FIB-4 score was $P = .42$, with adjustment for sex and BMI. *Bars* indicate 95% CIs; *Circle* indicates *PNPLA3* I148M reference allele homozygotes; *Triangle* indicates *PNPLA3* I148M heterozygotes; *Square* indicates *PNPLA3* I148M alternate allele homozygotes.

Similar association results for FIB-4 scores were observed in sensitivity analyses including all participants older than 18 years of age (Supplementary Tables 13 and 14), or after adjustment for diabetes (Supplementary Table 15). A parallel analysis assuming that participants with missing values had ALT and AST levels below the upper limit of normal and FIB-4 scores less than 2.67 showed similar results (Supplementary Tables 16 and 17).

## Discussion

This study evaluated the prevalence and clinical impact of liver disease–associated *HSD17B13* and *PNPLA3* variants in Hispanics/Latinos, who will comprise 30% of the US population within the next 3 decades and have a high prevalence of liver disease.[25,26] Previous studies have shown that the frequency of *PNPLA3* I148M across racial and ethnic groups correlates with NAFLD prevalence, and is highest in Hispanics/Latinos.[6,27] Population variation in the frequency of the protective *HSD17B13* rs72613567:TA splice variant also has been described: 34% in East Asian, 26% in White/European American, 10% in Hispanic/Latino, and 6% in Black/African American individuals.[27] This correlates inversely with population-specific risks for liver disease.[28,29] In the present study, we found that the allele frequency of *HSD17B13* and *PNPLA3* variants differed across genetic ancestry groups within a self-reported Hispanic/Latino patient population. Individuals with ancestry from Ecuador or Mexico had a low frequency of *HSD17B13* pLoF variants (10% and 7%, respectively) and a high frequency of the *PNPLA3* I148M risk variant (54% and 65%, respectively). Using EHR data, we found that *HSD17B13* pLoF variants were associated with lower liver enzyme levels and liver fibrosis risk, while *PNPLA3* I148M was associated with increased liver enzyme levels and fibrosis risk.

Differential rates of NAFLD across genetic ancestry groups within the Hispanic/Latino population are consistent with known genetic diversity of self-reported Hispanics/Latinos. Persons of Mexican and Central/South American descent have the highest prevalence of NAFLD, while other Hispanic/Latino subpopulations have a slightly lower prevalence than White/European Americans, even after adjusting for waist circumference, BMI, and insulin resistance, suggesting underlying genetic risk factors.[30–32] Most studies of genetic factors underlying liver disease in Hispanics/Latinos in the United States include individuals of Mexican descent, and have shown a high frequency of *PNPLA3 I148M* (49%),[6,27] and a low frequency of *HSD17B13* pLoF variants (10%–15%).[14,27] Our findings corroborate the existing literature describing higher *PNPLA3* I148M frequencies in populations from Mexico and Central/South American countries compared with other Hispanic/Latino subpopulations.[19,33–36] Individuals from Caribbean countries had similar frequencies for *HSD17B13* and *PNPLA3* variants as White/European American individuals.

Limitations of our study included possible selection bias because Bio*Me* participants are recruited from a hospital-based ambulatory care setting and may not be representative of the general population. In addition, participants with available outpatient liver enzyme levels may be more likely to have underlying liver disease, resulting in some ascertainment bias. However, an additional analysis assuming normal values in those untested showed similar results. Although the study did not include liver biopsy data, longitudinal changes in noninvasive measures of fibrosis are known to identify those at risk of severe liver disease and liver-related events.[22,37] The study cohort included participants with all non-viral etiologies of CLD because the genes investigated are known to affect the risk of multiple etiologies of liver disease.[10,11,38] However, we performed a sensitivity analysis excluding participants with AUD or etiologies of CLD other than NAFLD. We did not include socioeconomic factors in our analyses given the limitations of EHR data to assess these. Strengths included an ancestrally diverse and unselected cohort with a high proportion of Hispanics/Latinos with origins from Caribbean countries, and our approach leveraging genetic ancestry and real-world longitudinal EHR data.

Understanding the role of genetic risk factors in diverse populations can improve screening, prevention, and early identification of liver disease.[39] There remains much to be understood about the interplay between genes and clinical risk factors, particularly in diverse populations who are under-represented in genomic

studies and biobanks.[40] Our study addresses an important disparity in the United States because Hispanics/Latinos have among the highest rates of obesity and liver disease, but less access to care than other racial and ethnic groups.[41] Hispanic/Latino individuals in the Unites States also have more advanced liver disease at the time of liver transplant listing.[42] The effective identification of Hispanic/Latino individuals at highest risk for liver fibrosis will enable us to target those in need of screening and interventions.

## Conclusions

Using a genome-first approach, we surveyed the frequency of the *PNPLA3* I148M risk variant and protective *HSD17B13* pLoF variants across Hispanics/Latinos in an EHR-linked biobank. We noted variations in frequency of *HSD17B13* and *PNPLA3* variants between ancestral groups, which may contribute to differences in liver disease risk. Ongoing studies will improve our understanding of genomic risk in the prevention and management of liver disease in diverse populations, including high-risk Hispanics/Latinos in the United States.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.12.025.

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**Conflicts of interest**
These authors disclose the following: Eimear E. Kenny has received personal fees from Regeneron Pharmaceuticals, 23andMe, and Illumina, and has served on the advisory boards for Encompass Biosciences and Galateo Bio; and Noura S. Abul-Husn is an employee and equity holder of 23andMe, serves as a scientific advisory board member for Allelica, has received personal fees from Genentech, Allelica, and 23andMe, has received research funding from Akcea, and previously was employed by Regeneron Pharmaceuticals. The remaining authors disclose no conflicts.

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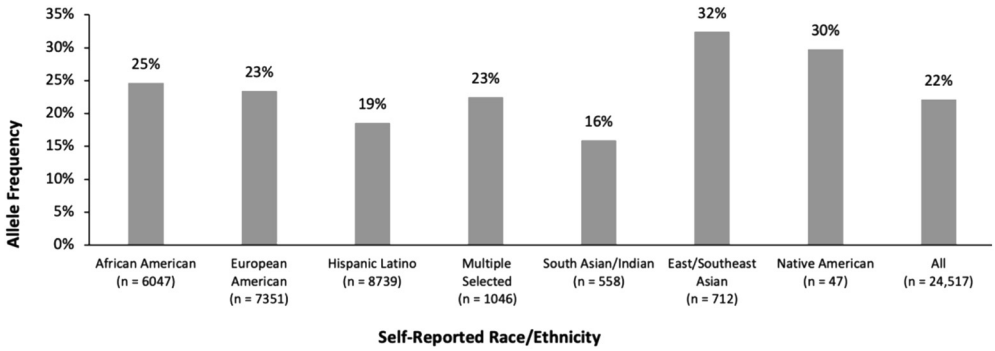


**Supplementary Figure 1.** Minor allele frequency of all predicted loss-of-function variants in *HSD17B13* in unrelated participants of Bio*Me* by self-reported race and ethnicity. "Multiple Selected" signifies that the participant selected more than one race/ethnicity category.

**Supplementary Table 1.** ICD-9/ICD-10 Codes for Alcohol Use Disorder or Etiologies of Chronic Liver Disease Other Than NAFLD

| Diagnosis | ICD-9 | ICD-10 |
|---|---|---|
| Chronic hepatitis B infection | 070.22, 070.23, 070.32, 070.33 | B18.0, B18.1, B19.1 |
| Chronic hepatitis C infection | 070.44, 070.54, 070.7 | B18.2, B19.2 |
| Alcohol-associated liver disease | 571.0–571.3 | K70.0, K70.1, K70.10, K70.11, K70.2, K70.3, K70.30, K70.31, K70.4, K70.40, K70.41, K70.9 |
| Alcohol use disorder | 291, 303.0, 305.0, 303.9 | F10.x |
| Hemochromatosis | 275.01 | E83.11, E83.119 |
| Primary biliary cholangitis | 571.6 | K74.3, K74.5 |
| Primary sclerosing cholangitis | 576.1 | K83.0 |
| Autoimmune hepatitis | 571.42 | K75.4 |
| $\alpha$-1-antitrypsin deficiency | 273.4 | E88.01 |
| Sarcoidosis | 135 | D86.9 |
| Secondary malignant neoplasm of liver and intrahepatic bile duct | 197.7 | C78.7 |
| Secondary biliary cirrhosis | No available code | K74.4 |
| Wilson's disease | 275.1 | E83.00, E83.01, E83.09 |

ICD-9, International Classification of Diseases, 9th revision; ICD-10, International Classification of Diseases, 10th revision; NAFLD, nonalcoholic fatty liver disease.

**Supplementary Table 2.** Demographic and Clinical Characteristics of Unrelated, Adult Hispanics/Latinos From the Bio*Me* Biobank by *HSD17B13* pLoF Variants (0/1/2) Genotype Status

| Genotype status (*HSD17B13* pLoF variants) | 0 (n = 5404) | 1 (n = 3082) | 2 (n = 253) |
|---|---|---|---|
| Demographic/clinical features | | | |
| Age at enrollment, *y*, mean (SD) | 51.6 (16.4) | 52.2 (16.2) | 53.3 (16.96) |
| Female sex, n (%) | 3,301 (61.1) | 1,977 (64.2) | 152 (60.1) |
| BMI, $kg/m^2$, median (IQR) | 28.4 (24.9–33.1) | 28.7 (24.9–33.3) | 28.7 (24.8–32.3) |
| DM2, n (%)[a] | 1562 (32.4) | 970 (35.4) | 97 (42.7) |
| HTN, n (%)[a] | 3016 (55.8) | 1818 (59.0) | 156 (61.7) |
| Median outpatient ALT level, *U/L*, median (IQR)[a] | 20.5 (15–30) | 20.0 (15–28) | 21.0 (16–27) |
| Median outpatient AST level, *U/L*, median (IQR)[a] | 22.0 (18–28) | 21.0 (18–27) | 21.5 (18–27) |
| Most recent FIB-4 score, median (IQR) | 1.16 (0.76–1.78) | 1.14 (0.76–1.73) | 1.15 (0.81–1.77) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM2, type 2 diabetes mellitus; FIB-4, Fibrosis-4 score; HTN, hypertension; IQR, interquartile range; pLoF, predicted loss-of-function.
[a]$P < .05$ with Kruskal–Wallis equality-of-populations rank test between genotype groups.

**Supplementary Table 3.** Demographic and Clinical Characteristics of Unrelated, Adult Hispanics/Latinos From the Bio*Me* Biobank by *PNPLA3* I48M (0/1/2) Genotype Status

| Genotype status (*PNPLA3* I48M) | 0 (n = 3906) | 1 (n = 3671) | 2 (n = 1032) |
|---|---|---|---|
| Demographic/clinical features | | | |
| Age at enrollment, *y*, mean (SD) | 51.8 (16.4) | 52.2 (16.5) | 51.1 (15.5) |
| Female sex, n (%)[a] | 2471 (63.3) | 2275 (62.0) | 599 (58.0) |
| BMI, $kg/m^2$, median (IQR) | 28.6 (24.8–33.3) | 28.5 (26.0–33.0) | 28.4 (25.0–32.9) |
| DM2, n (%) | 1143 (33.2) | 1151 (34.9) | 306 (32.9) |
| HTN, n (%)[a] | 2250 (57.6) | 2148 (58.5) | 531 (51.5) |
| Median outpatient ALT level, *U/L*, median (IQR)[a] | 19.5 (15–27) | 20 (15.5–29.5) | 23.5 (16.5–36) |
| Median outpatient AST level, *U/L*, median (IQR)[a] | 21 (18–26) | 22 (18–28) | 23.5 (19–32) |
| Most recent FIB-4 score, median (IQR)[a] | 1.12 (0.74–1.69) | 1.18 (0.78–1.80) | 1.18 (0.77–1.93) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM2, type 2 diabetes mellitus; FIB-4, Fibrosis-4 score; HTN, hypertension; IQR, interquartile range.
*$P < .05$ with Kruskal–Wallis equality-of-populations rank test between genotype groups.

**Supplementary Table 4.** Demographic and Clinical Characteristics of Unrelated, Adult Hispanics/Latinos With Available FIB-4 Scores

| Characteristic | Hispanics/Latinos with FIB-4 scores (n = 4960) |
|---|---|
| Age at most recent laboratory test, *y*, mean (SD) | 59.7 (13.9) |
| Age group, *y*, n (%) | |
| 35–50 | 1406 (28.4) |
| 51–65 | 1832 (36.9) |
| >65 | 1722 (34.7) |
| Female sex, n (%) | 3246 (65.6) |
| BMI, $kg/m^2$, median (IQR) **(n = 4346)** | 29.1 (25.4–33.4) |
| Most recent FIB-4 score, median (IQR) | 1.2 (0.9–1.7) |
| Most recent FIB-4 score >2.67, n (%) | 405 (8.2) |
| Time between FIB-4 scores, *y*, mean (SD) **(n = 3852)** | 7.4 (4.4) |
| Change in FIB-4/year, median (IQR) **(n = 3852)** | 0.03 (-0.01 to 0.07) |

NOTE. All sample sizes = 4960 unless otherwise indicated in bold.
BMI, Body mass index; FIB-4, Fibrosis-4 score; IQR, interquartile range.

**Supplementary Table 5.** Minor Allele Frequency of 9 pLoF Variants in *HSD17B13* in Hispanics/Latinos

| cDNA position | MAF | rsID | Variant type |
|---|---|---|---|
| c.773_774del | 0.000 | – | Frameshift |
| c.602C>G | 0.000 | rs142648167 | Stop gained |
| c.573del | 0.059 | rs80182459 | Frameshift |
| c.450G>A | 0.006 | rs61748262 | Stop gained |
| c.371dup | 0.000 | rs1333905019 | Frameshift |
| c.294_298del | 0.002 | rs540096704 | Frameshift |
| c.226del | 0.000 | rs1390900187 | Frameshift |
| c.175C>T | 0.000 | rs376596440 | Stop gained |
| – | 0.149 | rs72613567 | Splice variant |
| All pLOF variants | 0.204 | Multiple | Multiple |

NOTE. cDNA position provided for NM_178135.5.
cDNA, complementary DNA; MAF, minor allele frequency; pLoF, predicted loss-of-function.

**Supplementary Table 6.** Associations of *HSD17B13* pLoF Variants With ALT, AST, FIB-4 Score, Advanced Fibrosis (FIB-4 >2.67), and Change in FIB-4 Score Over Time by Genetic Ancestry Group

| Population | ALT | | AST | | FIB-4 | | FIB-4 >2.67 | | Change in FIB-4/y | |
|---|---|---|---|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4/change in FIB-4 analyses | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | OR (95% CI) | *P* value | β coefficient (SE) | *P* value |
| All Hispanics/Latinos (n = 4910/4856/4150/3777) | -0.08 (0.03) | .002[a] | -0.10 (0.03) | <.001[a] | -0.05 (0.03) | .045[a] | 0.92 (0.76–1.13) | .44 | 0.02 (0.03) | .41 |
| Colombia (n = 43/42/35/31) | -0.42 (0.27) | .12 | -0.62 (0.24) | .01[a] | -0.39 (0.43) | .36 | N/A | N/A | -0.37 (0.48) | .45 |
| Dominican Republic (n = 669/662/520/458) | -0.04 (0.06) | .53 | -0.07 (0.06) | .25 | -0.07 (0.07) | .34 | 1.54 (0.95–2.51) | .08 | -0.03 (0.04) | .50 |
| Ecuador (n = 179/180/154/152) | -0.12 (0.20) | .56 | -0.10 (0.18) | .59 | 0.13 (0.18) | .46 | 3.02 (1.09–8.36) | .03[a] | 0.04 (0.12) | .73 |
| Mexico (n = 66/65/47/43) | -0.05 (0.32) | .87 | 0.49 (0.39) | .22 | 0.71 (0.30) | .02[a] | N/A | N/A | 0.28 (0.06) | <.001[a] |
| Other Central/South American (n = 307/305/271/256) | -0.16 (0.12) | .18 | 0.04 (0.13) | .77 | 0.11 (0.12) | .36 | 1.10 (0.60–2.00) | .76 | -0.03 (0.04) | .52 |
| Puerto Rico (n = 3283/3240/2841/2625) | -0.03 (0.03) | .33 | -0.07 (0.03) | .02[a] | -0.08 (0.03) | .01[a] | 0.63 (0.48–0.83) | .001[a] | -0.04 (0.04) | .38 |

NOTE. ALT and AST linear regression models were adjusted for age, sex, and body mass index. FIB-4 linear (most recent FIB-4 score) and logistic (FIB-4 >2.67) regression models were adjusted for sex and BMI. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; OR, odds ratio; pLoF, predicted loss-of-function.

[a]Significant values ($P < .05$).

**Supplementary Table 7.** Associations of *PNPLA3* I148M With ALT, AST, FIB-4 Score, Advanced Fibrosis (FIB-4 >2.67), and Change in FIB-4 Score Over Time by Genetic Ancestry Group

| Population | ALT | | AST | | FIB-4 | | FIB-4 >2.67 | | Change in FIB-4/year | |
|---|---|---|---|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4/change in FIB-4 analyses | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | OR (95% CI) | *P* value | β coefficient (SE) | *P* value |
| All Hispanics/Latinos (n = 4910/4856/4150/3777) | 0.16 (0.02) | <.001[a] | 0.16 (0.02) | <.001[a] | 0.08 (0.02) | <.001[a] | 1.35 (1.15–1.59) | <.001[a] | 0.04 (0.05) | .35 |
| Colombia (n = 43/42/35/31) | -0.03 (0.25) | .91 | -0.04 (0.24) | .86 | -0.31 (0.26) | .23 | 0.19 | .31 | 0.01 (0.33) | .97 |
| Dominican Republic (n = 669/662/520/458) | -0.07 (0.06) | .24 | -0.02 (0.06) | .69 | 0.04 (0.06) | .52 | 1.17 (0.75–1.83) | .48 | 0.02 (0.04) | .67 |
| Ecuador (n = 179/180/154/152) | 0.17 (0.12) | .14 | 0.24 (0.10) | .02[a] | 0.36 (0.11) | .001[a] | 4.14 (1.47–11.66) | .007[a] | 0.12 (0.08) | .13 |
| Mexico (n = 66/65/47/43) | 0.24 (0.18) | .17 | 0.26 (0.18) | .16 | -0.07 (0.18) | .70 | N/A | N/A | -0.01 (0.04) | .82 |
| Other Central/South American (n = 307/305/271/256) | 0.12 (0.09) | .20 | 0.06 (0.10) | .57 | -0.03 (0.09) | .76 | 1.13 (0.69–1.86) | .62 | 0.03 (0.03) | .33 |
| Puerto Rico (n = 3283/3240/2841/2625) | 0.18 (0.03) | <.001[a] | 0.18 (0.03) | <.001[a] | 0.08 (0.3) | .004[a] | 1.32 (1.07–1.62) | .01[a] | -0.05 (0.04) | .13 |

NOTE. ALT and AST linear regression models were adjusted for age, sex, and body mass index. FIB-4 linear (most recent FIB-4 score) and logistic (FIB-4 >2.67) regression models were adjusted for sex and body mass index. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; OR, odds ratio.
[a]Significant values ($P < .05$).

**Supplementary Table 8.** Associations of Multiplicative Interaction Term Between *HSD17B13* pLoF Variants and *PNPLA3* I148M With ALT, AST, FIB-4 Score, Advanced Fibrosis (FIB-4 >2.67), and Change in FIB-4 Score Over Time by Genetic Ancestry Group

| Population | ALT | | AST | | FIB-4 | | FIB-4 >2.67 | | Change in FIB-4/year | |
|---|---|---|---|---|---|---|---|---|---|---|
| n = participants for ALT/AST/ FIB-4/change in FIB-4 analyses | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | OR (95% CI) | *P* value | β coefficient (SE) | *P* value |
| All Hispanics/Latinos (n = 4910/ 4856/4150/3777) | -0.11 (0.04) | .006[a] | -0.05 (0.04) | .18 | -0.03 (0.04) | .42 | 1.23 (0.91–1.68) | .17 | -0.02 (0.03) | .44 |
| Colombia (n = 43/42/35/31) | 0.18 (0.38) | .64 | 0.16 (0.33) | .64 | 0.72 (0.82) | .38 | N/A | N/A | 1.45 (1.05) | .18 |
| Dominican Republic (n = 669/662/ 520/458) | -0.05 (0.10) | .64 | -0.07 (0.10) | .49 | -0.06 (0.10) | .56 | 0.92 (0.46–1.84) | .81 | -0.04 (0.06) | .55 |
| Ecuador (n = 179/180/154/152) | 0.17 (0.35) | .63 | 0.79 (0.31) | .01[a] | 0.76 (0.32) | .02[a] | 11.96 (0.92–154.63) | .06 | 0.24 (0.22) | .27 |
| Mexico (n = 66/65/47/43) | 0.41 (0.47) | .39 | -0.23 (0.51) | .64 | 0.67 (0.63) | .29 | N/A | N/A | -0.24 (0.11) | .045[a] |
| Other Central/South American (n = 307/305/271/256) | -0.20 (0.21) | .34 | 0.04 (0.24) | .88 | -0.48 (0.22) | .03[a] | 0.23 (0.07–0.72) | .01 | -0.09 (0.07) | .22 |
| Puerto Rico (n = 3283/3240/2841/ 2625) | -0.10 (0.05) | .03[a] | -0.06 (0.05) | .21 | 0.10 (0.05) | .0496[a] | 1.41 (0.94–2.12) | .10 | 0.06 (0.06) | .31 |

NOTE. ALT and AST linear regression models were adjusted for age, sex, and body mass index. FIB-4 linear (most recent FIB-4 score) and logistic (FIB-4 >2.67) regression models were adjusted for sex and body mass index. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; OR, odds ratio; pLoF, predicted loss-of-function.

[a]Significant values ($P < .05$).

**Supplementary Table 9.** Associations of *HSD17B13* pLoF Variants With ALT, AST, and FIB-4 Score Overall and by Genetic Ancestry Group After Excluding Those With ICD-9/ICD-10 Codes for Alcohol Use Disorder or Chronic Liver Disease Other Than NAFLD

| Population | ALT | | AST | | FIB-4 | | FIB-4 >2.67 | |
|---|---|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4 analyses | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | OR (95% CI) | *P* value |
| All Hispanics/Latinos (n = 4600/4531/3745) | -0.07 (0.03) | .005[a] | -0.11 (0.03) | <.001[a] | -0.07 (0.03) | .01[a] | 0.95 (0.75–1.19) | .63 |
| Colombia (n = 41/42/34) | -0.42 (0.27) | .14 | -0.58 (0.19) | .004[a] | -0.40 (0.34) | .25 | N/A | N/A |
| Dominican Republic (n = 652/640/468) | -0.10 (0.06) | .12 | -0.17 (0.06) | .006[a] | -0.03 (0.07) | .67 | 1.69 (0.97–2.93) | .06 |
| Ecuador (n = 172/168/144) | -0.17 (0.22) | .43 | -0.23 (0.19) | .24 | -0.15 (0.17) | .38 | 1.45 (0.33–6.31) | .62 |
| Mexico (n = 56/53/36) | -0.06 (0.33) | .86 | 0.47 (0.44) | .29 | 0.52 (0.33) | .12 | N/A | N/A |
| Other Central/South American (n = 299/300/262) | -0.13 (0.12) | .28 | 0.10 (0.13) | .46 | 0.09 (0.13) | .48 | 1.75 (0.99–3.09) | .05 |
| Puerto Rico (n = 3106/3058/2592) | -0.008 (0.03) | .81 | -0.06 (0.03) | .04[a] | -0.10 (0.03) | .003[a] | 0.66 (0.49–0.89) | .007[a] |

NOTE. ALT and AST linear regression models were adjusted for age, sex and body mass index. FIB-4 linear (most recent FIB-4 score) and logistic (FIB-4 >2.67) regression models were adjusted for sex and body mass index. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; ICD-9/ICD-10, International Classification of Diseases, 9th revision/International Classification of Diseases, 10th revision; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 10.** Associations of *PNPLA3* I148M With ALT, AST, and FIB-4 Score Overall and by Genetic Ancestry Group After Excluding Those With ICD-9/ICD-10 Codes for Alcohol Use Disorder or Chronic Liver Disease Other Than NAFLD

| Population | ALT | | AST | | FIB-4 | | FIB-4 >2.67 | |
|---|---|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4 analyses | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | OR (95% CI) | *P* value |
| All Hispanics/Latinos (n = 4600/4531/3745) | 0.15 (0.02) | <.001[a] | 0.16 (0.02) | <.001[a] | 0.06 (0.02) | .02[a] | 1.26 (1.05–1.51) | .01[a] |
| Colombia (n = 41/42/34) | -0.08 (0.25) | .76 | -0.05 (0.19) | .79 | -0.24 (0.19) | .22 | N/A | N/A |
| Dominican Republic (n = 652/640/468) | -0.04 (0.06) | .43 | -0.02 (0.05) | .67 | 0.06 (0.06) | .33 | 1.23 (0.74–2.04) | .43 |
| Ecuador (n = 172/168/144) | 0.20 (0.13) | .12 | 0.24 (0.11) | .03[a] | 0.21 (0.10) | .04[a] | 4.27 (1.10–16.54) | .04[a] |
| Mexico (n = 56/53/36) | 0.15 (0.19) | .44 | 0.20 (0.22) | .37 | -0.08 (0.19) | .67 | 1.46 (0.09–23.19) | .79 |
| Other Central/South American (n = 299/300/262) | 0.13 (0.10) | .17 | 0.05 (0.11) | .63 | -0.07 (0.10) | .49 | 0.87 (0.51–1.48) | .62 |
| Puerto Rico (n = 3106/3058/2592) | 0.18 (0.03) | <.001[a] | 0.19 (0.03) | <.001[a] | 0.08 (0.03) | .009[a] | 1.34 (1.06–1.69) | .01[a] |

NOTE. ALT and AST linear regression models were adjusted for age, sex, and body mass index. FIB-4 linear (most recent FIB-4 score) and logistic (FIB-4 >2.67) regression models were adjusted for sex and body mass index. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; ICD-9/ICD-10, International Classification of Diseases, 9th revision/International Classification of Diseases, 10th revision; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.
[a]Significant values ($P < .05$).

**Supplementary Table 11.** Associations of Multiplicative Interaction Term Between *HSD17B13* pLoF Variants and *PNPLA3* I148M With ALT, AST, and FIB-4 Score Overall and by Genetic Ancestry Group After Excluding Those With ICD-9/ICD-10 Codes for Alcohol Use Disorder or Chronic Liver Disease Other Than NAFLD

| Population | ALT | | AST | | FIB-4 | | FIB-4 >2.67 | |
|---|---|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4 analyses | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | OR (95% CI) | *P* value |
| All Hispanics/Latinos (n = 4600/4531/3745) | -0.11 (0.04) | .008[a] | -0.07 (0.04) | .09 | 0.08 (0.05) | .08 | 1.15 (0.82–1.63) | .42 |
| Colombia (n = 41/42/34) | 0.23 (0.38) | .54 | 0.16 (0.26) | .55 | 0.36 (0.65) | .59 | N/A | N/A |
| Dominican Republic (n = 652/640/468) | 0.0004 (0.10) | .99 | -0.05 (0.09) | .63 | -0.09 (0.11) | .41 | 0.80 (0.36–1.75) | .57 |
| Ecuador (n = 172/168/144) | 0.13 (0.42) | .76 | 0.30 (0.37) | .42 | -0.37 (0.34) | .27 | 1.67 (0.07–37.11) | .75 |
| Mexico (n = 56/53/36) | 0.41 (0.50) | .42 | -0.36 (0.58) | .54 | -0.20 (0.74) | .79 | N/A | N/A |
| Other Central/South American (n = 299/300/262) | -0.21 (0.21) | .32 | 0.04 (0.34) | .88 | -0.38 (0.22) | .09 | 0.40 (0.13–1.18) | .10 |
| Puerto Rico (n = 3106/3058/2592) | -0.11 (0.05) | .02[a] | -0.07 (0.05) | .14 | 0.14 (0.06) | .01[a] | 1.40 (0.88–2.20) | .15 |

NOTE. ALT and AST linear regression models were adjusted for age, sex and body mass index. FIB-4 linear (most recent FIB-4 score) and logistic (FIB-4 >2.67) regression models were adjusted for sex and body mass index. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; ICD-9/ICD-10, International Classification of Diseases, 9th revision/International Classification of Diseases, 10th revision; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 12.** Associations of *HSD17B13* pLoF Variants, *PNPLA3* I148M, and Multiplicative Interaction Term Between *HSD17B13* pLoF Variants and *PNPLA3* I148M With FIB-4 Score Across by Age Bins

| | *HSD17B13* pLoF variants | | *PNPLA3* I148M | | Interaction between *HSD17B13* pLoF variants and *PNPLA3 I148M* | |
|---|---|---|---|---|---|---|
| Age group, *y*, n (%) | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value | β coefficient (SE) | *P* value |
| All ages, 4866 (100) | -0.06 (0.03) | .02[a] | 0.05 (0.02) | .01[a] | 0.01 (0.04) | .84 |
| 18–34 years, 488 (10) | -0.06 (0.04) | .08 | -0.01 (0.03) | .84 | -0.08 (0.05) | .12 |
| 35–50 years, 1087 (22.3) | -0.02 (0.02) | .50 | 0.04 (0.02) | .05 | -0.03 (0.04) | .42 |
| 51–65 years, 1574 (32.4) | -0.01 (0.02) | .66 | 0.03 (0.02) | .02[a] | 0.02 (0.04) | .54 |
| >65 years, 1717 (35.3) | -0.06 (0.02) | .008[a] | 0.05 (0.02) | .009[a] | 0.03 (0.04) | .44 |

NOTE. FIB-4 score linear regression model was adjusted for sex and body mass index.
FIB-4, Fibrosis-4 score; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 13.** Associations of *HSD17B13* pLoF Variants, *PNPLA3* I148M, and Multiplicative Interaction Term Between *HSD17B13* pLoF Variants and *PNPLA3* I148M With FIB-4 Score in Participants Older Than 18 Years of Age

| Population | *HSD17B13* pLoF variants | | *PNPLA3 I148M* | | Interaction between *HSD17B13* pLoF variants and *PNPLA3 I148M* | |
|---|---|---|---|---|---|---|
| n = participants for FIB-4 analysis | $\beta$ coefficient (SE) | *P* value | $\beta$ coefficient (SE) | *P* value | $\beta$ coefficient (SE) | *P* value |
| All Hispanics/Latinos (n = 4866) | -0.06 (0.03) | .02[a] | 0.05 (0.02) | .01[a] | 0.01 (0.04) | .84 |
| Colombia (n = 42) | -0.57 (0.29) | .06 | -0.41 (0.23) | .09 | 0.07 (0.39) | .86 |
| Dominican Republic (n = 635) | -0.05 (0.07) | .47 | 0.06 (0.06) | .33 | 0.03 (0.11) | .81 |
| Ecuador (n = 183) | 0.24 (0.18) | .19 | 0.34 (0.10) | <.001[a] | 0.46 (0.30) | .13 |
| Mexico (n = 64) | 0.04 (0.27) | .87 | -0.08 (0.15) | .60 | 0.78 (0.38) | .04[a] |
| Other Central/South American (n = 308) | 0.12 (0.11) | .27 | -0.03 (0.08) | .67 | -0.32 (0.19) | .27 |
| Puerto Rico (n = 3344) | -0.08 (0.03) | .01[a] | 0.04 (0.03) | .16 | -0.01 (0.05) | .87 |

NOTE. FIB-4 score linear regression model was adjusted for sex and body mass index.
FIB-4, Fibrosis-4 score; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 14.** Associations of *HSD17B13* pLoF Variants, *PNPLA3* I148M, and Multiplicative Interaction Term Between *HSD17B13* pLoF Variants and *PNPLA3* I148M With Advanced Fibrosis (FIB-4 > 2.67) in Participants Older Than 18 Years of Age

| Population | *HSD17B13* pLoF variants | | *PNPLA3 I148M* | | Interaction between *HSD17B13* pLoF variants and *PNPLA3 I148M* | |
|---|---|---|---|---|---|---|
| n = participants for FIB-4 analysis | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| All Hispanics/Latinos (n = 4866) | 0.92 (0.63–1.36) | .68 | 1.67 (1.25–2.23) | .001[a] | 0.91 (0.57–1.45) | .70 |
| Colombia (n = 42) | N/A | N/A | 1.10 (0.05–22.24) | .95 | N/A | N/A |
| Dominican Republic (n = 635) | 1.48 (0.60–3.65) | .40 | 1.40 (0.66–2.97) | .38 | 0.62 (0.17–2.23) | .46 |
| Ecuador (n = 183) | 0.95 (0.09–10.51) | .97 | 2.19 (0.64–7.44) | .21 | 0.47 (0.01–16.94) | .68 |
| Mexico (n = 64) | N/A | N/A | 1.32 (0.33–5.25) | .69 | N/A | N/A |
| Other Central/South American (n = 308) | 1.10 (0.31–3.85) | .89 | 1.21 (0.58–2.54) | .61 | 0.89 (0.25–3.20) | .86 |
| Puerto Rico (n = 3344) | 0.94 (0.54–1.61) | .81 | 1.68 (1.07–2.63) | .02[a] | 1.19 (0.64–2.21) | .58 |

NOTE. FIB-4 score logistic regression model was adjusted for sex and body mass index. N/A indicates that we were unable to calculate the odds ratio owing to collinearity.
FIB-4, Fibrosis-4 score; OR, odds ratio; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 15.** Associations of *HSD17B13* pLoF Variants, *PNPLA3 I148M*, and Multiplicative Interaction Term Between *HSD17B13* pLoF Variants and *PNPLA3* I148M With FIB-4 Score, After Adjustment for Type 2 Diabetes

| Population | *HSD17B13* pLoF variants | | *PNPLA3* I148M | | Interaction between *HSD17B13* pLoF variants and *PNPLA3 I148M* | |
|---|---|---|---|---|---|---|
| n = participants for FIB-4 analysis | $\beta$ coefficient (SE) | *P* value | $\beta$ coefficient (SE) | *P* value | $\beta$ coefficient (SE) | *P* value |
| All Hispanics/Latinos (n = 4866) | -0.06 (0.03) | .03[a] | 0.06 (0.02) | .005[a] | 0.003 (0.04) | .94 |
| Colombia (n = 42) | -0.54 (0.39) | .07 | -0.35 (0.25) | .17 | -0.18 (0.42) | .67 |
| Dominican Republic (n = 630) | -0.06 (0.07) | .33 | 0.07 (0.06) | .24 | 0.06 (0.11) | .56 |
| Ecuador (n = 176) | 0.24 (0.18) | .18 | 0.35 (0.10) | <.001[a] | 0.46 (0.30) | .14 |
| Mexico (n = 64) | 0.05 (0.27) | .86 | -0.08 (0.15) | .61 | 0.84 (0.39) | .03[a] |
| Other Central/South American (n = 299) | 0.12 (0.11) | .26 | -0.03 (0.08) | .67 | -0.32 (0.19) | .10 |
| Puerto Rico (n = 3344) | -0.08 (0.03) | .01[a] | 0.04 (0.03) | .09 | -0.02 (0.05) | .73 |

NOTE. FIB-4 score linear regression model was adjusted for sex, type 2 diabetes, and body mass index.
FIB-4, Fibrosis-4 score; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 16.** Associations of *HSD17B13* pLoF Variants With ALT and AST Increase and Advanced Fibrosis (FIB-4 >2.67) by Genetic Ancestry Group

| Population | ALT ≥45 IU/L | | AST ≥35 IU/L | | FIB-4 >2.67 | |
|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4 | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| All Hispanics/Latinos (n = 7790) | 0.82 (0.67–0.99) | .049[a] | 0.86 (0.72–1.02) | .08 | 0.93 (0.76–1.14) | .47 |
| Colombia (n = 130) | N/A | N/A | N/A | N/A | N/A | N/A |
| Dominican Republic (n = 1689) | 1.14 (0.73–1.78 | .56 | 0.96 (0.66–1.40) | .84 | 1.33 (0.84–2.01) | .23 |
| Ecuador (n = 386) | 0.67 (0.28–1.61) | .37 | 0.92 (0.44–1.94) | .83 | 1.17 (0.49–2.80) | .72 |
| Mexico (n = 214) | 0.61 (0.14–2.69) | .51 | 0.53 (0.12–2.37) | .40 | N/A | N/A |
| Other Central/South American (n = 709) | 0.87 (0.44–1.70) | .68 | 0.85 (0.48–1.52) | .59 | 0.91 (0.47–1.79) | .79 |
| Puerto Rico (n = 4120) | 0.90 (0.68–1.18) | .45 | 0.96 (0.76–1.22) | .73 | 0.85 (0.64–1.12) | .24 |
| Other (n = 542) | 0.71 (0.31–1.61) | .41 | 0.72 (0.35–1.47) | .36 | 1.29 (0.55–3.04) | .56 |

NOTE. Missing values of ALT and AST were coded as ALT <45 IU/L and AST <35 IU/L, respectively. Missing values of FIB-4 were coded as FIB-4 ≤2.67. Logistic regression models were adjusted for sex. N/A indicates that we were unable to calculate the odds ratio owing to lower cases numbers.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; OR, odds ratio; pLoF, predicted loss-of-function.
[a]Significant values ($P < .05$).

**Supplementary Table 17.** Associations of *PNPLA3* I148M With ALT and AST Increase and Advanced Fibrosis (FIB-4 >2.67) by Genetic Ancestry Group

| Population | ALT ≥45 IU/L | | AST ≥35 IU/L | | FIB-4 >2.67 | |
|---|---|---|---|---|---|---|
| n = participants for ALT/AST/FIB-4 | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| All Hispanics/Latinos (n = 7668) | 1.76 (1.44–2.15) | <.0001[a] | 1.61 (1.36–1.91) | <.0001[a] | 1.66 (1.35-2.05) | <.0001[a] |
| Colombia (n = 123) | N/A | N/A | N/A | N/A | N/A | N/A |
| Dominican Republic (n = 1675) | 1.52 (0.97–2.37) | .07 | 1.26 (0.87–1.83) | .22 | 1.68 (1.06–2.68) | .03[a] |
| Ecuador (n = 373) | 1.38 (0.61–3.11) | .44 | 1.50 (0.70–3.23) | .30 | 2.86 (0.86–9.53) | .09 |
| Mexico (n = 207) | 1.16 (0.31–4.37) | .83 | 1.28 (0.36–4.58) | .70 | N/A | N/A |
| Other Central/South American (n = 691) | 1.39 (0.73–2.65) | .32 | 2.19 (1.20–3.98) | .01[a] | 1.54 (0.78–3.02) | .21 |
| Puerto Rico (n = 4016) | 1.68 (1.26–2.23) | .0004[a] | 1.58 (1.23–2.01) | .0003[a] | 1.43 (1.08–190) | .01[a] |
| Other (n = 538) | 1.71 (0.78–3.72) | .18 | 1.31 (0.66–2.59) | .44 | 1.93 (0.82–4.54) | .13 |

NOTE. Missing values of ALT and AST were coded as ALT <45 IU/L and AST <35 IU/L, respectively. Missing values of FIB-4 were coded as FIB-4 ≤2.67. Logistic regression models were adjusted for sex. N/A indicates that we were unable to calculate the odds ratio owing to lower cases numbers.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 score; OR, odds ratio.
[a]Significant values ($P < .05$).