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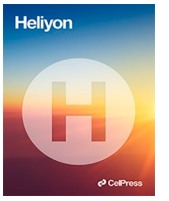

Research article

Selection scan in Native Americans of Mexico identifies *FADS2* rs174616: Evidence of gene-diet interactions affecting lipid levels and Delta-6-desaturase activity

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ABSTRACT

Searching for positive selection signals across genomes has identified functional genetic variants responding to environmental change. In Native Americans of Mexico, we used the fixation index (F_{st}) and population branch statistic (PBS) to identify SNPs suggesting positive selection. The 103 most differentiated SNPs were tested for associations with metabolic traits, the most significant association was *FADS2*/rs174616 with body mass index (BMI). This variant lies within a linkage disequilibrium (LD) block independent of previously reported *FADS* selection signals and has not been clearly associated with metabolic phenotypes. We tested this variant in two independent cohorts with cardiometabolic data. In the Genetics of Atherosclerotic Disease (GEA) cohort, the derived allele (T) was associated with increased BMI, lower LDL-C levels and a decreased risk of subclinical atherosclerosis in women. Significant gene-diet interactions affected lipid, apolipoprotein and adiponectin levels with differences according to sex, involving mainly total and complex dietary carbohydrate%. In the Genotype-related Effects of PUFA trial, the derived allele was associated with lower Δ-6 desaturase activity and erythrocyte membrane dihomo-gamma-linolenic acid (DGLA) levels, and with increased Δ-5 desaturase activity and eicosapentaenoic acid levels. This variant interacted with dietary carbohydrate% affecting Δ-6 desaturase activity. Notably, the relationship of DGLA and other erythrocyte membrane LC-PUFA indices with HOMA-IR differed according to rs174616 genotype, which has implications regarding how these indices should be interpreted. In conclusion, this observational study identified rs174616 as a signal suggesting selection in an independent linkage disequilibrium block, was associated with cardiometabolic and erythrocyte measurements of LC-PUFA in two independent Mexican cohorts and showed significant gene-diet interactions.

1. Introduction

Genomic studies identifying genetic variations associated with complex traits in different populations have made important contributions to the understanding of the genetic architecture and biological bases of human disease. It is well documented however, that even large-scale genomic studies have not captured global diversity because they are predominantly based on populations of European ancestry [1]. More than a decade after the first genome wide association studies (GWAS) were published, the underrepresentation of non-European populations in these studies has become a public health and a scientific concern, as this bias has important implications for risk prediction of diseases across populations. Most individuals included in GWAS aiming to identify genetic risk variants associated with complex traits are European (78 %), but only 1.3 % are Hispanic or Latin American [2]. A reduced number of GWAS in Latino or Hispanic populations have been conducted to seek variants associated with type 2 diabetes (T2D) [3], blood lipid levels [4,5], serum uric acid levels [6], and various anthropological traits such as skin pigmentation and human facial variation in the Candela Consortium [7–10]. In the Mexican population, genomic studies have identified novel gene variants associated with metabolic traits, such as *SLC16A11* variants associated with T2D [3], and the *ABCA1* R230C and *SIDT2* V636I variants associated with high density lipoprotein (HDL-C) levels and premature coronary artery disease [5,11,12].

While the success of hypothesis-free approaches for gene discovery in complex traits is unquestionable, hypothesis-driven approaches can also be used to further unravel the genetic architecture of complex disease. As human populations have been shaped by evolutionary forces (genetic drift, founder effects and natural selection), evolutionary approaches seeking positive selection signals across the genome have identified genetic variation that is functional and responds to environmental change [13–16]. The Mexican population of today is the result of complex and ongoing admixture processes, and of demographic and adaptive processes that have health implications [17]. While large sample sizes are required to identify robust associations, an evolutionary approach using genotype data and phenotype data is a promising strategy to identify gene variation affecting the health of the Mexican and possibly other Latin American populations of today. Using these methods, in recent years a large number of articles have identified variants with positive selection in genes such as *SCL24A5* involved in skin pigmentation [18], *EDAR* and *EDAR2* involved in the development of hair follicles in Asia, LARGE and DMD involved in Lassa virus infection in West Africa [19], the melanocortin 3 receptor gene associated with obesity and insulin resistance [20], the *SIK3* gene associated with high triglyceride (TG) levels in the Mexican population [13], as well as PPARG and AJAP1, both negative regulators of the Wnt/β catenin signaling pathway in Native Americans of Mexico [21]. Notably, several independent studies in various populations have identified different positive selection signals within genes of the *FADS* family involved in fatty acid metabolism, that point to a complex evolutionary scenario of human adaptation to different geographic environments and to diet [22–29].

We used the fixation index (F_{st}) and population branch statistic (PBS) to identify the most differentiated genetic variants suggesting positive selection and tested these variants for associations with anthropometric and blood lipid traits in a discovery cohort of Native American populations of Mexico. Because the rs174616 variant, within the *FADS* gene cluster, showed the most significant association with a metabolic trait in Native Americans, we also tested this variant in two independent cohorts of the Mexican population: the Mexican Genetics of Atherosclerotic Disease (GEA) Cohort and the Genotype-Related Effects of Polyunsaturated Fatty Acids (GREPUFA) Trial, seeking associations with cardiometabolic and Ω-3 and Ω-6 long chain poly-unsaturated fatty acid (LC-PUFA) parameters, as well as gene-diet interactions affecting these traits.

2. Materials and methods

The design of this observational study is summarized in Supplementary Fig. 1.

2.1. Study populations

Discovery Cohort: Native Americans from Mexico (NATAM): A total of 466 Native American individuals with SNP 6.0 microarray data were included in a selection scan using F_{st}: 165 Nahuas and 98 Totonacs from the State of Puebla; 100 Zapotecs from Oaxaca and 103 Mayans from Campeche, Quintana Roo and Yucatan. All participants from these groups identified themselves as belonging to their respective Native American group, were born in their local communities and spoke their Native language. All NATAM individuals included in this study were previously described by Romero-Hidalgo et al., 2017 [17,30].

Genetics of Atherosclerotic Disease (GEA) Mexican Cohort: This cohort was designed to study the genetic bases of premature coronary artery disease (CAD) and cardiovascular risk factors in the Mexican population, all participants were recruited, and all clinical measurements were performed at the Instituto Nacional de Cardiología "Ignacio Chávez". The present study included 1570 individuals recruited as controls without a personal or family history of premature CAD, and 1200 premature CAD cases. Mean ages were 53.30 ± 9.36 and 54.18 ± 8.15 years in controls and cases respectively, with 49.18 % male controls and 80.05 % male cases. Recruitment strategy, inclusion criteria, anthropometric and biochemical characteristics have been previously described [12].

Genotype-related Effects of PUFA Trial (GRE-PUFA Trial): This cohort (NCT02296385) included 165 Mexican individuals (36.97 % male) recruited from the UNAM and the Universidad Iberoamericana in Mexico City, aged 18–40 years (mean age 26.59 ± 6.25 years), with BMI ≥18.5 and <30 kg/m2 and without type 2 diabetes (T2D). Participants received daily oral supplementation with 3 fish oil capsules containing 647 mg of eicosapentaenoic acid (EPA) and 253 mg of docosahexaenoic acid (DHA) (daily intake: 2.7 g/day of DHA and EPA in fish oil) for 6 weeks. Inclusion and exclusion criteria, dietary supplementation and anthropometric and biochemical assessment were previously described [31]. Briefly, the study consisted of 3 visits: visit 1 or baseline, where blood samples were drawn for biochemical measurements, and questionnaires for physical activity, medication and/or supplementation use were collected; visit 2 (3 weeks after V1), where anthropometric measurements were assessed; and visit 3 (6 weeks after V1), where the physical activity and medication and/or supplementation use questionnaires were collected and blood samples were drawn again for biochemical measurements. Compliance with treatment was assessed according to the number of returned capsules and treatment days.

2.2. Ethics Statement

The study complied with the principles of the Declaration of Helsinki and was approved by the Research and Ethics Committees of all participant institutions: Instituto Nacional de Medicina Genómica (INMEGEN), Instituto Nacional de Cardiología "Ignacio Chávez", Universidad Nacional Autónoma de México (UNAM) and Western Institutional Review Board. The GRE-PUFA trial was registered at the clinical.trials.gov database with the number NCT02296385 (https://clinicaltrials.gov/ct2/show/NCT02296385). All participants provided written informed consent prior to inclusion in the study. For Native American participants a translator was used as needed.

2.3. Dietary assessment

Food Frequency Questionnaires (FFQ) previously validated for the Mexican population by the Instituto Nacional de Salud Pública [32] were applied to GEA and GRE-PUFA Trial participants. Energy intake and the proportion of macronutrients consumed were estimated using the system evaluation of nutritional habits and food intake (SNUT software) [33]. Dietary macronutrient percentages were estimated as the percentage of total energy (kilocalories) supplied by each macronutrient. Dietary habits were not assessed in the NATAM cohort.

2.4. Cardiometabolic and erythrocyte LC-PUFA measurements

For all 3 cohorts, blood samples were drawn after 8–12 h of overnight fasting to determine the serum levels of glucose, insulin, total cholesterol (TC), TG, HDL-C and low-density lipoprotein cholesterol (LDL-C) by standardized methods as previously described [12,31]. In the GEA cohort, other cardiometabolic parameters including serum ApoA, ApoB, total adiponectin and liver enzyme levels, visceral abdominal fat to subcutaneous abdominal fat (VAT/SAT) ratio and Agatston coronary artery calcification score were measured as previously described [12,34]. In GRE-PUFA Trial participants, blood erythrocytes were isolated by centrifugation at 2100 g g for 15 min at 4 °C, and lipids were extracted using the method described by Folch [35]. The concentrations of twenty-seven fatty acids in erythrocyte membranes were measured via gas chromatography at Omegametrix GmGH Laboratory (Germany). The enzymatic activities of Delta 5 desaturase and Delta 6 desaturase were estimated as the product-to-precursor ratios: arachidonic acid (AA, 20:4n–6)/dihomo-gamma-linolenic acid (DGLA,20:3n–6); and gamma-linolenic acid (GLA, 18:3n–6)/Linoleic acid (LA,18:2n–6), respectively [36,37]. HS-Ω-3 index results are given as EPA + DHA expressed as a percentage of total identified FA after response factor correction (based on correlation curves).

2.5. Genotyping and quality control

Genomic DNA was isolated from peripheral white blood cells of participants from all 3 cohorts using standard methods. In the

discovery cohort, genotyping was performed in the microarray core facility of INMEGEN using Affymetrix SNP 6.0. Standard quality control (QC) filters were applied to remove SNPs and/or individuals using Plink v1.07 [38]. Only SNPs with call rate >95 % were included, while SNPs with minor allele frequency (MAF) < 5 % and/or deviation from Hardy Weinberg equilibrium ($P < 1x10^{-5}$) were excluded. Samples showing sex discordance or identity-by-descent (IBD) were also excluded. A total of 397,789 SNPs were considered for the analyses after QC measures.

2.6. Ancestry analysis

Global ancestry was estimated using microarray genotype data as previously described [17]. Briefly, European (CEU) and Yoruba (YRI) individuals from the 1000 genomes project and fourteen Nahua and Totonac trios (Native American or NATAM) were used as reference populations for ancestry analyses. Multidimensional scaling components were calculated with Plink. Ancestral proportions were determined with Admixture [39]. Local ancestry was determined to identify chromosomal segments of European or African origin using PCAadmix [40]. Chromosome phasing was performed using Beagle 3.1 [41]. Inferred European segments with a probability ≥80 % based on the estimates of local ancestry were masked for the selection scan.

2.7. Selection scan

Wright's F_{st} and PBS (Population Branch Statistics) were used to identify the variants most differentiated between Native American and reference populations [42,43]. For this purpose, we included data from 170 Asian individuals [CHB (Chinese Han from Beijing) and JPT (Japanese from Tokyo)] and 112 individuals of European descent (CEU) from the 1000 genomes project as populations of comparison, making 3 distinct comparisons: 1) F_{st} (CHB + JPT vs. NAT), 2) F_{st} (CEU vs. NAT) and 3) PBS (NAT vs. CHB + JPT, CEU). Variants with differentiation values above percentile 99.99 were tested for associations with anthropometric and biochemical parameters in the discovery cohort. We depicted the most differentiated variants based on F_{st} and PBS with Manhattan plots. Wright's F_{st} values range from 0 (no differentiation) to 1 (complete differentiation), we used a $-1/(\log_{10}F_{st})$ transformation for $0<F_{st}<1$.

2.8. Association analyses

The 103 variants with the highest differentiation values were tested for associations with body mass index (BMI), and serum TG, HDL-C, LDL-C and TC levels in the discovery cohort (NATAM), using mixed linear models with the EMMAX software [44] adjusting for age, sex, components 1 and 2, and BMI as appropriate. All traits were log10 transformed for the analysis. Components C1 and C2 were obtained from a multidimensional scaling analysis performed with Plink. Finally, a meta-analysis using the METAL program [45] was performed to combine the results from the four Native American populations.

Associations of *FADS2* rs174616 with anthropometric and biochemical measurements were tested in the GEA and GRE-PUFA Trial participants using generalized linear models, adjusting for age, BMI and Native American ancestry proportion in GEA, and for age, sex and BMI in GRE-PUFA participants. Variables from both cohorts without normal distribution according to the Shapiro-Wilk test were log-transformed for the analyses. False Discovery Rate was used to correct for multiple hypothesis testing (FDR <0.05).

2.9. Gene-diet interactions

Pearson's correlations were calculated to study the linear relationship between normalized variables and dietary macronutrient proportions stratified by rs174616 genotype in both cohorts, and also by sex in the GEA cohort. In the GRE-PUFA Trial, correlations of erythrocyte measurements of Ω-3 and Ω-6 LC-PUFA status with clinical parameters were tested and stratified by genotype. Generalized linear models were used to assess interactions between rs174616 genotypes and both dietary (energy supply for macronutrients) and

Table 1
Clinical characteristics and global ancestry proportions (NATAM, EUR and AFR) in Native American groups included in the discovery cohort.

	Mayan (n = 103)	Nahua (n = 165)	Totonac (n = 98)	Zapotec (n = 100)	*P*
Age	42.9 ± 14.0	46.4 ± 14.3	54.6 ± 13.3	35.3 ± 20.5	[b]
Men, %	9.7	32.1	77.6	45.0	[b]
BMI, kg/m^2	30.0 ± 4.8	26.3 ± 4.4	27.0 ± 4.4	25.9 ± 4.4	[b]
TG, mg/dL	204.6 ± 119.5	176.6 ± 87.1	190.0 ± 89.0	184.7 ± 106.5	NS
TC, mg/dL	179.7 ± 40.1	178.2 ± 55.5	183.6 ± 31.7	192.1 ± 47.0	NS
HDL-C, mg/dL	41.7 ± 9.6	40.1 ± 12.3	41.3 ± 9.6	41.3 ± 12.1	NS
LDL-C, mg/dL	106.8 ± 31.0	101.2 ± 27.6	103.6 ± 28.5	99.2 ± 31.4	NS
NATAM Component, %	85.7 ± 10.4	89.9 ± 10.4	91.8 ± 11.8	89.1 ± 11.1	[b]
EUR Component, %	11.5 ± 9.7	9.0 ± 9.7	6.9 ± 11.1	9.1 ± 9.7	[a]
AFR Component, %	2.8 ± 2.0	1.1 ± 0.9	1.3 ± 0.9	1.8 ± 1.8	[b]

Differences among groups were compared with ANOVA. BMI: body mass index, TG: triglycerides, TC: total cholesterol, HDL-C: high density lipoproteins-cholesterol, LDL-C: low density lipoprotein cholesterol; EUR: European; AFR: African; NS: Not significant.

[a] $P < 0.05$.

[b] $P < 0.001$.

erythrocyte measurements of Ω-3/Ω-6 LC-PUFA status adjusting for age and sex. Native American ancestry estimation was included as covariate in the GEA cohort. False Discovery Rate (FDR <0.05) was used to correct for multiple testing. In accordance with the observed correlation patterns, dominant "T" allele and additive models were tested. Statistical calculations and graphs were made using R [46].

3. Results

3.1. Ancestry analysis

Table 1 shows the demographic characteristics, lipid parameters and mean ancestry proportions of Native American individuals included in the discovery cohort. The global ancestry analysis of the reference populations and the Native American discovery cohort is shown in Supplementary Fig. 2. The mean NATAM ancestry proportion ranged from 85.7 ± 10.4 % in Mayans to 91.8 ± 11.8 in Totonacs. Notably, the EUR component was >20 % in 12 % of NATAM individuals. Thus, local ancestry estimations were used to identify and remove EUR and AFR chromosomal segments for the selection scan. Comparative multidimensional scaling (MDS) plots of components 1 and 2, with and without EUR/AFR segments are shown in Supplementary Fig. 3.

3.2. Selection scan

Fig. 1 shows Manhattan plots for F_{st} and PBS analyses. Altogether, a total of 103 variants surpassed the 99.99 differentiation percentile threshold (Supplementary Table 1). Twenty-eight were intronic variants within protein coding genes including *EDAR*, *ADAMTS9*, *SLC45A2* and *FADS2*, one was a *SLC45A2* 3′UTR variant, 14 were located within long non-coding RNA genes, 60 were intergenic.

3.3. Genetic associations with cardiometabolic traits

3.3.1. Discovery cohort

The 103 most differentiated variants were then tested for associations with anthropometric (BMI) and serum lipid levels in Native American individuals from the discovery cohort (Fig. 2). The most statistically significant association was observed between *FADS2* rs174616 and BMI ($P = 0.028$). This SNP lies within intron 7 of the *FADS2* gene (C/T), and the derived "T" allele frequency varied from 89 % in Zapotecs to 99 % in Mayans. Notably, "T" allele frequency was 94 % in NATAM, 47 % in EUR and 19 % East Asians (CHB + JPT) and was found to be associated with increased BMI in this group under the additive model (β = 1.73 %, 95 % CI: 0.19 %, 3.27 %; $P = 0.028$).

3.3.2. GEA cohort (Mexican Mestizos)

The general characteristics and genotype frequencies of GEA participants are described in Supplementary Table 2. The derived "T" allele frequency was 0.73. Fig. 3 shows the associations of rs174616 with metabolic parameters under the additive model in GEA participants recruited as controls with and without stratification by sex. Interestingly, the "T" allele was associated with increased BMI only in women (β = 1.16 %, 95 % CI: 0.24 %, 2.07 %; $P = 0.0138$). The "T" allele was also associated with lower LDL-C levels in the overall analysis (β = −2.8 %, 95 % CI: 5.2 %, −0.4 %; $P = 0.02$), and in women β = −3.8 %, 95 % CI: 7.2 %, −0.3 %; $P = 0.032$), but not in men ($P = 0.311$). Moreover, the "T" allele was associated with decreased risk of subclinical atherosclerosis (coronary calcium score >0) only in women (OR = 0.557; 95 % CI: 0.377–0.823; $P = 0.003$). After adjusting for age, BMI and NATAM ancestry proportion, this variant was not significantly associated with premature CAD in the entire GEA cohort or in any sex group. Only the association with

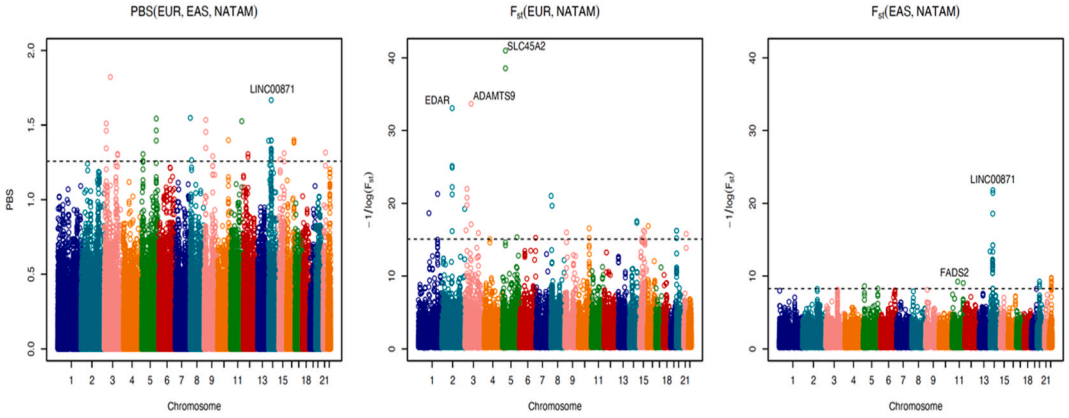

Fig. 1. PBS and F_{st} Manhattan plots comparing EUR, EAS and NATAM populations. Dotted line indicates the threshold for the top 0.01 % most differentiated SNPs.

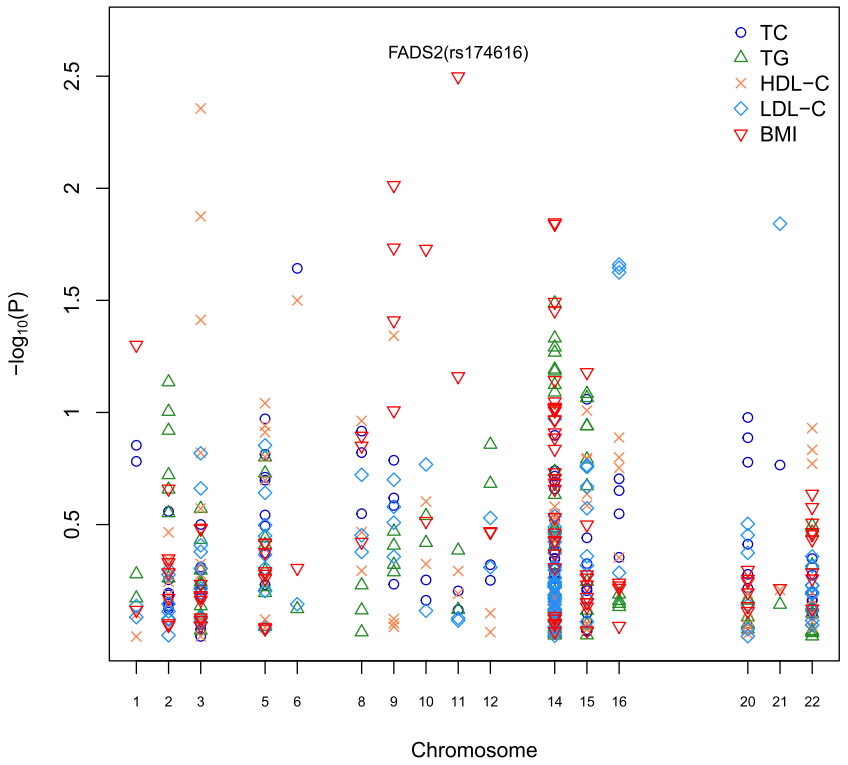

Fig. 2. Manhattan plot shows the meta-analysis of associations of the 103 most differentiated genetic variants with body mass index and serum lipid levels in the discovery cohort. BMI: body mass index, TC: total cholesterol, TG: triglycerides, HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol.

subclinical atherosclerosis in women remained significant after FDR correction ($P < 0.05$).

3.3.3. *GRE-PUFA trial cohort*

"T" allele frequency in the GRE-PUFA trial was also 0.73. At baseline (V1), no significant associations with anthropometric parameters, homeostasis model of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c) or serum lipid levels were observed in PUFA trial participants. However, the derived "T" allele was significantly associated with decreased erythrocyte Δ6Des activity (β = −4.20 %, 95 % CI: 6.47 %, −1.93 %; $P = 3.9\text{x}10^{-4}$), increased erythrocyte Δ5Des activity (β = 5.24 %, 95 % CI: 2.73 %, 7.75 %; $P = 6.7\text{x}10^{-5}$), decreased DGLA levels and arachidonic to eicosapentaenoic acid (AA/EPA) ratio (β = −4.75 %, 95 % CI: 6.94 %, −2.55 %; $P = 3.8\text{x}10^{-5}$ and β = −4.63 %, 95 % CI: 8.34 %, −0.92 %; $P = 0.15$, respectively), and with increased EPA levels (β = 5.01 %, 95 % CI: 1.39 %, 8.62 %; $P = 0.007$). Associations with AA/EPA ratio did not reach statistical significance after FDR correction (Fig. 4, Supplementary Table 3).

3.4. *Gene-diet interactions*

3.4.1. *GEA cohort*

Fig. 5 shows correlations between dietary and cardiometabolic parameters stratified by rs174616 genotype in GEA control participants. These correlations varied in magnitude, direction, and significance, and showed differences according to sex and genotype (Supplementary Fig. 4). Generalized linear models revealed several gene-diet interactions that remained statistically significant after correction for multiple testing, which showed the highest level of significance under the dominant "T" allele model (TT + CT vs CC). Correlation differences according to genotype are only described for gene-diet interactions with P interaction values (P_{inter}) < 0.05 after FDR.

In women, significant rs174616-diet interactions modulated serum levels of TG, HDL-C, adiponectin, ApoB and ApoB/ApoA ratio under the dominant "T" allele model (Fig. 5A). For all significant interactions, the direction of the correlations between dietary parameters and metabolic traits was opposite in women with the derived "CT/TT" as compared to the ancestral "CC" genotype. TG levels correlated negatively with total dietary carbohydrate (CHO) and complex carbohydrate (coCHO) percentages ($P_{inter} = 0.0026$ and 0.0052, respectively); while HDL-C levels correlated positively with CHO and coCHO%, and negatively with total dietary fat% ($P_{inter} =$ 0.0007, 0.0027 and 0.0006, respectively) only in women with the ancestral "CC" genotypes. Moreover, ApoB/ApoA ratio correlated negatively with CHO and coCHO%, and positively with fat percentages only in the "CC" genotype group ($P_{inter} = 0.0024$, 0.0007 and 0.0009). While no significant gene-diet interactions were found to affect serum ApoA levels, a negative correlation of ApoB levels with

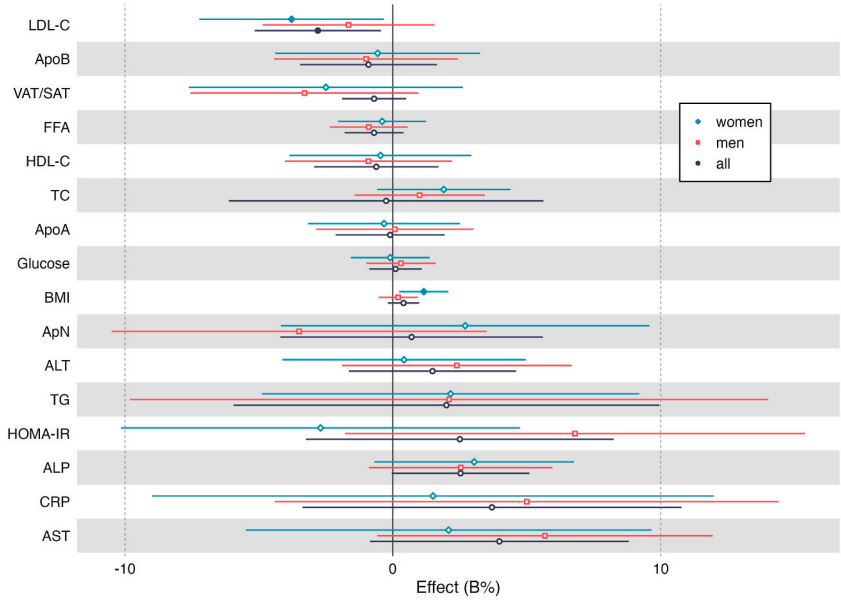

Fig. 3. Associations of the *FADS2* rs174616 "T" allele with metabolic parameters in GEA control participants in the entire cohort (ALL, in black) and stratified by sex, women in blue and men in red. Circles indicate the beta value of log-transformed data, lines represent 95 % confidence intervals. Dark circles indicate significant associations without correction for multiple testing. LDL-C: low density lipoprotein cholesterol; ApoB: apolipoprotein B; VAT/SAT: visceral to subcutaneous abdominal fat ratio; FFA: free fatty acids; HDL-C: high density lipoprotein-cholesterol; TC: total cholesterol; ApoA: apolipoprotein A; BMI: body mass index; ApN; adiponectin; ALT: alanine aminotransferase; TG: triglycerides; HOMA-IR: homeostasis model of insulin resistance; ALP: alkaline phosphatase; CRP: C reactive protein; AST: aspartate aminotransferase. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

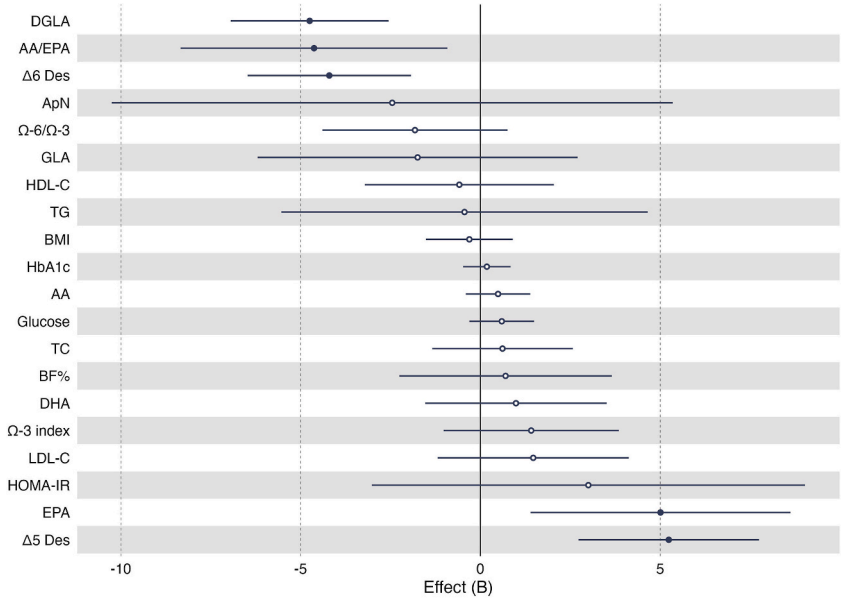

Fig. 4. Associations of the *FADS2* rs174616 "T" allele with metabolic parameters in GRE-PUFA Trial participants. Circles indicate the β value of log-transformed data, lines represent 95 % confidence intervals. Dark circles indicate significant associations without correction for multiple testing. DGLA: Dihomo-gamma-linolenic acid; AA/EPA: arachidonic to eicosapentanoic acid ratio, Δ6Des: Delta-6-desaturase activity in erythrocyte membranes, ApN: adiponectin, GLA: gamma-linolenic acid, HDL-C: high density lipoprotein-cholesterol, TG: triglycerides, BMI: body mass index, HbA1c: hemoglobin A1c, BF%: body fat percentage, AA: arachidonic acid, TC: total cholesterol, DHA: docosahexaenoic acid, LDL-C: low density lipoprotein cholesterol, Ω-6/Ω-3: Omega 6 to Omega 3 fatty acid ratio, HOMA-IR: homeostasis model of insulin resistance, EPA: eicosapentaenoic acid, Δ5Des: Delta-5-desaturase activity in erythrocyte membranes.

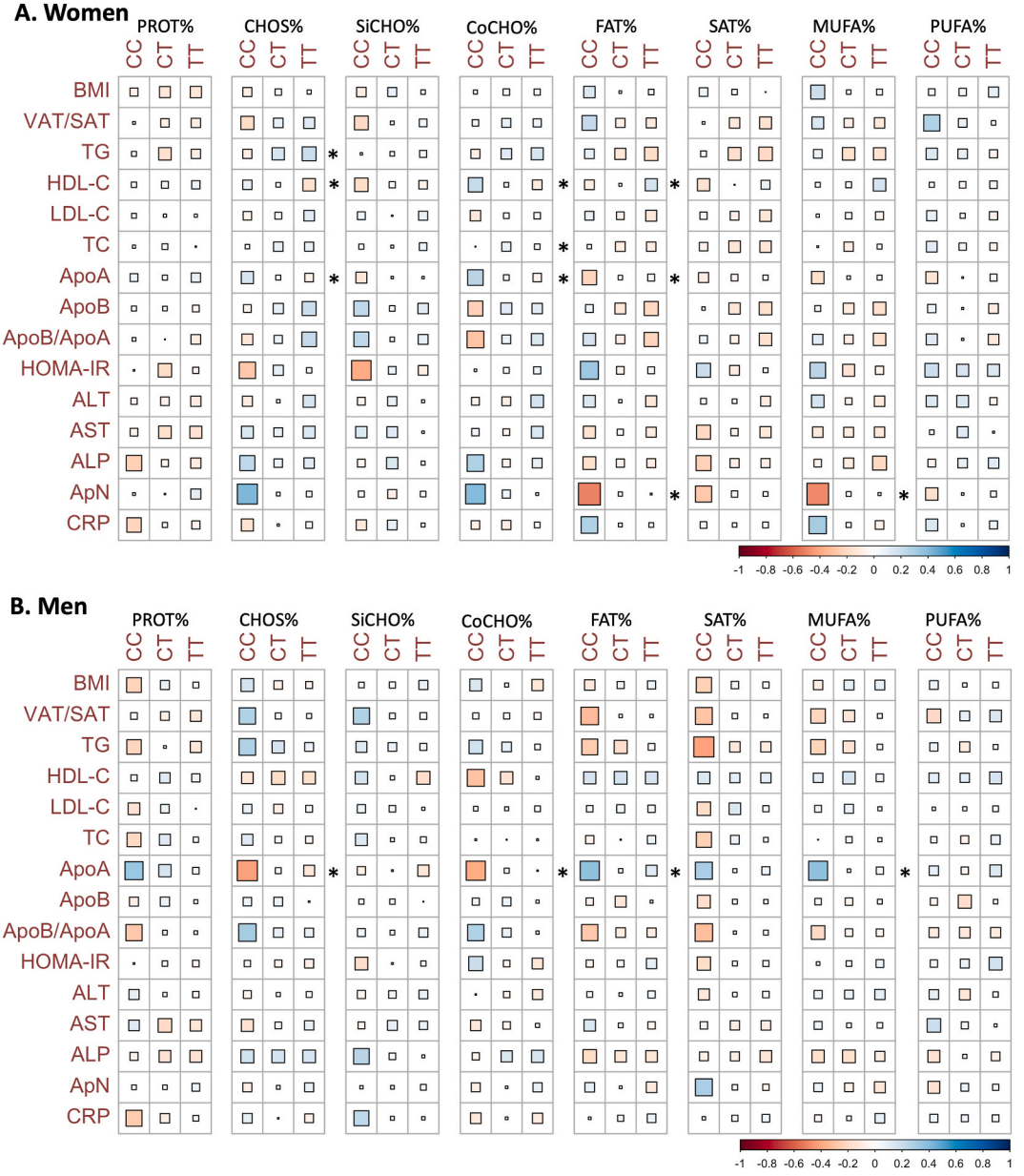

Fig. 5. Correlations between dietary macronutrient percentages and metabolic parameters in the GEA cohort, stratified by sex. A total of 841 individuals were TT homozygous (441 women, 400 men); 600 were CT heterozygous (297 women, 303 men) and 129 were CC homozygous (56 women, 73 men). The correlation matrix depicts positive correlations in blue and negative correlations in red. The color scale indicates estimated Pearson's correlation coefficient values, which are proportional to the size of the square. Gene-diet interactions under the "T" allele dominant model that remained statistically significant after adjusting for age and NATAM ancestry, and correction for multiple testing are indicated (*$P < 0.05$). BMI: body mass index, VAT/SAT: visceral to subcutaneous abdominal fat ratio,TG: triglycerides, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, ApoA: apolipoprotein A, ApoB: apolipoprotein B, HOMA-IR: homeostasis model of insulin resistance, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, ApN: adiponectin, FFA: free fatty acids, CRP: C- reactive protein; PROT%: dietary protein percentage; CHO%: total dietary carbohydrate percentage; SiCHO%: dietary simple carbohydrate percentage; CoCHO%: dietary complex carbohydrate percentage. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

complex carbohydrate % was found only in the ancestral "CC" genotype group ($P_{inter} = 0.0029$).

Notably, gene-diet interactions were also found to modulate serum adiponectin levels, as an inverse correlation of total adiponectin levels with total dietary fat% and MUFA% was observed only in the "CC" genotype group ($P_{inter} = 0.0012$ and $P_{inter} = 0.0014$ respectively). No significant interactions of rs174616 with total dietary protein, simple carbohydrate, saturated fat or PUFA

percentages were observed in women. Overall, rs174616-dietary component interactions show that women with the ancestral "CC" genotype showed more favorable metabolic profiles when the FFQ reported a higher proportion of dietary carbohydrates, and a less favorable metabolic profile with higher proportions of dietary fat.

In men, significant rs174616-diet interactions were found to modulate only serum ApoA levels (Fig. 5B). Only men with "CC" genotypes showed negative correlations of ApoA serum levels with total dietary carbohydrate and complex carbohydrate percentages (P_{inter} = 0.0004); and positive correlations of ApoA levels with total dietary fat% (P_{inter}<0.0008) and MUFA% (P_{inter}<0.0013). No significant interactions of rs174616 with total dietary protein%, simple carbohydrate, saturated fat or polyunsaturated fat (PUFA) % were observed in men after FDR correction. As observed in women, the strongest correlations were observed in men with the ancestral "CC" genotype. In contrast, a higher proportion of dietary carbohydrates and a lower proportion of dietary fats correlated with less favorable metabolic parameters in men with "CC" genotypes. Examples of these interactions in men and women are found in Supplementary Fig. 5.

3.4.2. GRE-PUFA trial

Because of the low number of "CC" individuals found in the PUFA Trial (n = 11) and the lower proportion of male participants (61/165, 37 %), all genetic analyses were performed using additive models and were not stratified by sex. Although correlations between macronutrients and anthropometric, lipid and glucose parameters varied according to genotype (Supplementary Fig. 6), no significant interactions between total dietary carbohydrate, fat or protein percentages and rs174616 affecting anthropometric parameters, serum lipid levels, glucose, HbA1c, HOMA-IR or adiponectin levels were observed (Fig. 6A). However, erythrocyte membrane Δ6Des activity was significantly modulated by dietary CHO% in this cohort, which correlated negatively in ancestral "CC" genotypes, and correlated positively in "TT" genotypes (P_{inter} = 0.0007, Fig. 6B).

Because PUFA trial participants received DHA dietary supplementation, we tested whether changes in metabolic parameters 6 weeks after receiving this supplement differed according to genotype. The "T" allele was associated with a greater decrease in glucose levels (β = −2.30 %, 95 % CI: 4.12 %, −0.47 %; P = 0.014) (Supplementary Fig. 7), however the association lost significance after FDR correction (P > 0.5). No other metabolic parameters differed significantly according to genotype in response to DHA supplementation.

3.5. Correlations of DGLA, Δ6Des and Δ5Des activity with metabolic parameters according to genotype

Overall, DGLA levels and erythrocyte Δ6Des activity showed positive correlations with BMI, body fat percentage and TG levels, while Δ5Des activity correlated negatively with these parameters. The direction of these correlations did not differ according to genotype (Fig. 7, Supplementary Fig. 8). Notably, the rs174616 genotype modulated the correlations of erythrocyte measurements of Ω-3 and Ω-6 PUFA status with HOMA-IR in a statistically significant manner after FDR correction (P_{inter}<0.05). Namely, in individuals with

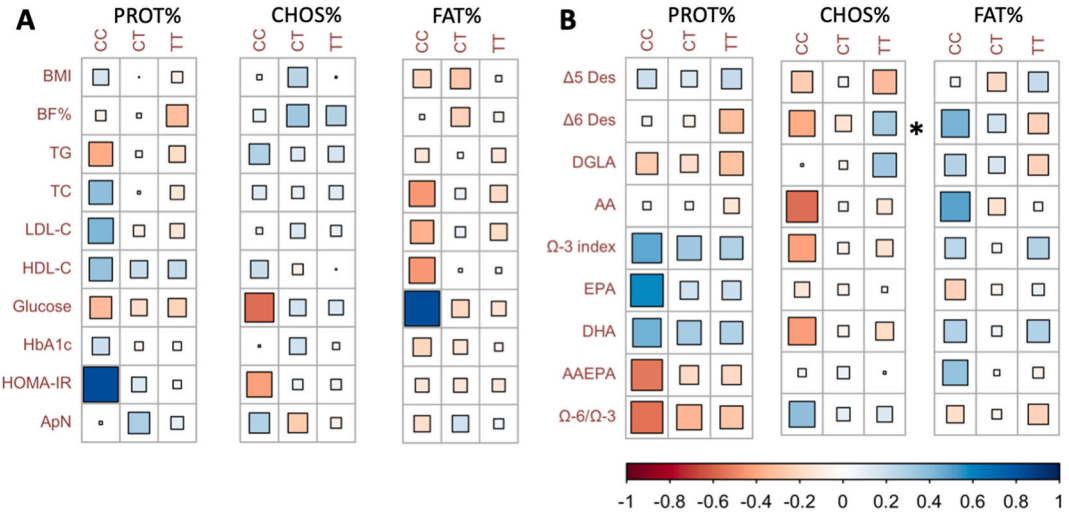

Fig. 6. Correlations of dietary macronutrient percentages with metabolic (A) and with Ω-3 and Ω-6 fatty acid (B) parameters in GRE-PUFA trial participants (n = 165: 11 CC, 66 CT and 88 TT). The correlation matrix depicts positive correlations in blue and negative correlations in red. The color scale indicates estimated Pearson's correlation coefficient values, which are proportional to the size of the square. Gene-diet interactions under the recessive model that remained statistically significant after adjusting for age and BMI and correction for multiple testing (FDR) are indicated (*P < 0.05). PROT%: dietary protein percentage, CHO%: total dietary carbohydrate percentage; FAT%: dietary fat percentage, BMI: body mass index, BF %: body fat percentage, TG: triglycerides, TC: total cholesterol, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein-cholesterol, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model of insulin resistance, ApN: adiponectin, Δ5Des: Delta-5-desaturase activity, Δ6Des: Delta-6-desaturase activity, DGLA: dihomo-gamma-linolenic acid; AA: arachidonic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, AA/EPA: arachidonic to eicosapentanoic acid ratio, Ω-6/Ω-3: Omega 6 to Omega 3 fatty acid ratio. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ancestral "CC" genotypes, HOMA-IR correlated positively with Δ5Des activity, Ω-3 index, EPA and DHA levels, while these correlations were negative in individuals with the derived "TT" genotype. In contrast, correlations of DGLA, AA/EPA and Ω-6/Ω-3 ratios were negative in "CC" genotypes, but positive in "TT" genotypes. These interactions affecting HOMA-IR are further described in Supplementary Fig. 9.

4. Discussion

Genetic evidence suggests that the FADS gene cluster has been targeted by selection multiple times in human history and in different populations, including Africans [22], Europeans [25,26,28,47], Eurasians [48], Greenlandic Inuit [23] and other Native Americans [24]. This positive selection is thought to be a response to diet adaptation, although the selective forces probably differed across time and in different geographical regions [26].

The *FADS1* and *FADS2* genes encode Δ-6 and Δ-5 desaturases respectively, involved in the Ω-6 and Ω-3 poly-unsaturated fatty acid synthesis pathways. Long-chain highly unsaturated metabolites (LC-PUFAs) such as DGLA (20:3n-6), AA (20:4n-6), EPA (20:5n-3) and DHA (22:6n-3) play a role in many biological functions. These LC-PUFAs are incorporated into membrane lipids affecting membrane fluidity, the activity of membrane and transport proteins, electrical excitation, and signal transmission [49–51], and are also precursors of prostaglandins, leukotrienes, thromboxanes and resolvins that mediate complex processes such as inflammation and platelet aggregation. LC-PUFAs also play a major role in carbohydrate, fatty acid, triglyceride, and cholesterol metabolism, by regulating the activity/abundance of different nuclear transcription factors such as peroxisome proliferator activated receptors, retinoid X receptors, liver X receptors, hepatic nuclear factors-4a, and sterol regulatory binding proteins [52]. Unsurprisingly, the effects of SNPs in the *FADS* gene cluster are highly pleiotropic, and according to the GWAS catalog [2] have been associated with a broad array of phenotypes including breast milk fatty acid composition, erythrocyte membrane fatty acid levels, lipidomic parameters, hematological parameters, psychiatric traits, metabolic traits (T2D, insulin resistance, fasting blood glucose, glycated hemoglobin, serum lipid levels, atherosclerosis, body weight, metabolic syndrome), inflammation-mediated diseases such as asthma and vitiligo. Very recently, *FADS* gene cluster variation has been associated with reproductive success, suggesting the *FADS* locus is unique in the sense that the selective sweep is still ongoing [53].

4.1. *FADS2* selection signal: rs174616 lies within an independent LD block

Most studies refer two different *FADS* gene cluster haplotypes known as A (ancestral) and D (derived) that include several SNPs that are not in LD [29]. However, rather than haplotypes, Mathieson [54] distinguished two independent LD blocks in this cluster: LDB1 spans *FADS1* and part of *FADS2*; minor allele frequencies of LDB1 SNPs increased gradually across populations from Africans to Europeans, East Asians, and became fixed in Native Americans (Fig. 8). LDB1 SNPs have been largely studied both for genetic associations and gene-diet interactions. In comparison, LDB2 spans part of *FADS2* and *FADS3,* has not been clearly associated with metabolic phenotypes and was described as a secondary signal of selection [54]. In the present study, we found evidence of selective pressure within LDB2 through F_{st} on comparing Native American and East Asian (CHB + JPT) populations. The derived rs174616 "T"

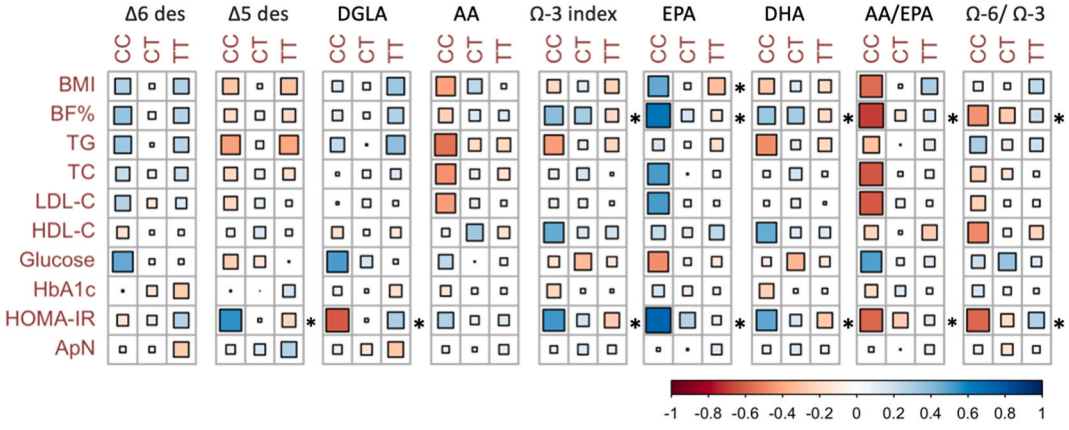

Fig. 7. Correlations of erythrocyte measurements of Δ6 and Δ5 desaturase activity and Ω-3 and Ω-6 fatty acids with metabolic parameters in GREPUFA trial participants (n = 165: 11 CC, 66 CT and 88 TT). The correlation matrix depicts positive correlations in blue and negative correlations in red. The color scale indicates estimated Pearson's correlation coefficient values, which are proportional to the size of the square. Interactions under the additive model that remained statistically significant after adjusting for age and BMI and correction for multiple testing (FDR) are indicated (*$P < 0.05$). BMI: body mass index, BF%: body fat percentage, TG: triglycerides, TC: total cholesterol, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein-cholesterol, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model of insulin resistance, ApN: adiponectin, Δ6Des: Delta-6-desaturase activity, Δ5Des: Delta-5-desaturase activity, DGLA: dihomo-gamma-linolenic acid; AA: arachidonic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, AA/EPA: arachidonic to eicosapentanoic acid ratio, Ω-6/Ω-3: Omega 6 to Omega 3 fatty acid ratio. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

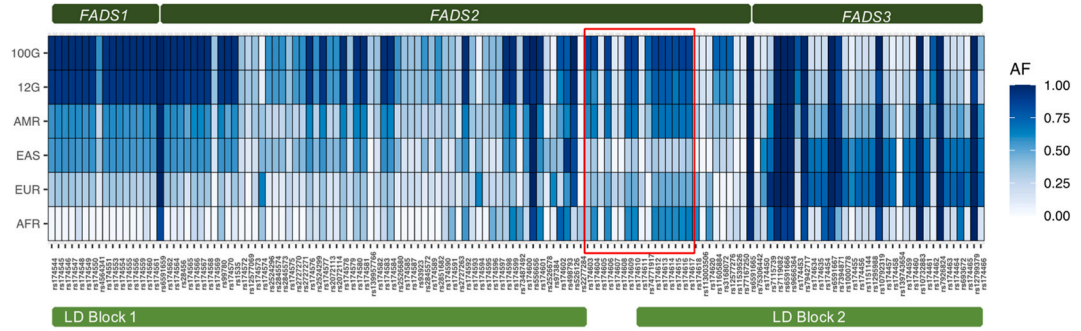

Fig. 8. Allele frequencies of FADS gene cluster variants across populations. Allele frequencies (AF) are represented for 1 KG populations (AFR: African, EUR: European, EAS East Asian and AMR (Americas, and in Native Americans of Mexico (12G: 12 genomes [17], 100G: 100genomes [45]). The top dark rectangles indicate the positions of *FADS1*, *FADS2* and *FADS3* genes. Green rectangles represent the two previously described linkage disequilibrium blocks LDB1 and LDB2. Rs174616 is found within LDB2. The group of SNPs found in high LD with rs174616 in Mexicans from 1 KG are indicated in the red rectangle. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

allele frequency is 17.9 % in CHB + JPT, 43.3 % in CEU and almost fixed (94.2 %) in NATAM individuals of Mexico. This variant is not in high LD with other FADS2 variants identified in previous selection scans in NATAM individuals ($r^2 \leq 0.4$) [23,24]. These studies may not have identified SNPs in LDB2 because their approach was a genome-wide scan for positive selection based on PBS values simultaneously comparing 3 populations (Native Americans, Europeans, and East Asians). In Mexican Americans from 1 KG, our lead SNP (rs174616) is in very high LD with 16 SNPs in the *FADS2* region ($r^2 = 0.83–1.0$), and the size of this LD block varies among 1 KG populations. As occurs with LDB1 SNPs, GTEx Portal shows that rs174616 and polymorphisms in high LD also affect the expression of *FADS1, FADS2, FADS3* and nearby genes in various tissues [55]. To our knowledge, this is the first time a signal suggesting natural selection has been identified in the LD block 2 described by Mathieson [54]. The lead SNP was associated with lipidomic/cardiometabolic parameters, showing evidence of gene-diet interactions in the Mexican population.

4.2. Associations with cardiometabolic and erythrocyte measurements of LC-PUFA status

In spite of the relatively low sample size, the rs174616 "T" allele was associated with increased BMI in Native American individuals. This association replicated only in women recruited as controls from the GEA cohort. Notably in this cohort, statistically significant associations of rs174616 with cardiometabolic parameters were only observed in women, as the "T" allele was also associated with lower LDL-C levels and a lower risk of subclinical atherosclerosis in this group. Because NATAM ancestry proportion was included as covariable, it is unlikely that these are caused by population stratification. Sex differences in associations with *FADS* gene cluster LDB1 SNPs have been previously reported [56]. Using an omics approach, Anderson et al. (2020) [57] identified six genes including *FADS1* showing sex differences in genetic regulation in adipose tissue. While there is mounting evidence that all adult tissues exhibit sex-specific expression patterns that are not always dependent of hormonal influence [58], it is yet unclear if the FADS gene cluster shows sex-specific expression or whether rs174616 is a sex-specific eQTL in different tissues.

While the GEA cohort was designed to identify genetic factors conferring susceptibility to premature CAD disease and cardiometabolic risk factors in the Mexican adult population [12], the GRE-PUFA trial aimed to analyze the effect of fish oil supplementation on glucose metabolism, circulating lipids and inflammation seeking gene-diet interactions [31]. This cohort is smaller and includes younger individuals without T2D or obesity. No significant associations with anthropometric or blood lipid parameters were observed in GRE-PUFA trial participants, however it showed very significant associations with erythrocyte measurements of LC-PUFA status: the rs174616 derived "T" allele, almost fixed in the Native American populations of Mexico, was significantly associated with lower DGLA and higher EPA levels in erythrocyte membranes, which is in line with decreased Δ6Des and increased Δ5Des activity in the PUFA synthesis pathway. Although AA levels were lower in individuals with the "T" allele in consistency with lower Δ5D activity, the association was not statistically significant. Moreover, the "T" allele was associated with a decreased AA/EPA ratio.

FADS gene cluster variation is highly pleiotropic and has been previously associated with lipid levels, lipidomic parameters, HOMA-IR, BMI, T2D, LC-PUFAs and many other traits, mostly for SNPs within LDB1. However, while no association of rs174616 with any type of trait is reported in the GWAS catalog, recent GWAS have found associations of variants in high LD with this SNP ($r^2 > 0.860$ in Mexicans) with lipidomic parameters, Ω-3 and Ω-6 PUFA and trans fatty acid levels, TG levels, body height and sexual dimorphism [59–64]. Moreover, a few candidate gene studies have reported that the rs174616 "T" allele was associated with decreased risk of T2D and decreased AA/LA ratio in the Chinese Han population [65], and with lower plasma AA levels and lower Δ5Des activity in Serbians [66]. Thus, although most of the scientific literature refers to LDB1 SNP associations, previous studies and our data show that SNPs from LDB2 also show pleiotropy, are associated with lipidomic and cardiometabolic parameters and show sex differences.

4.3. Dietary carbohydrates interact with rs174616 affecting cardiometabolic parameters

Several studies have reported interactions between FADS1/FADS2 gene variation in LD Block 1 and diet, comparing the effect of different diet interventions, PUFA supplementation, or dietary ALA/LA ratio assessed by FFQ on a wide array of phenotypes or outcomes, in individuals with different ages and health traits [67]. Several studies have reported significant interactions, mainly of FADS genotypes with dietary fatty acid composition and LC-PUFA supplementation [68–73].

The GEA study has previously reported gene-diet interactions that have been replicated in independent cohorts [74,75]. On seeking rs174616-diet interactions, two observations stand out: firstly, sex differences were observed as these interactions affected plasma lipid parameters (HDL-C, TG, ApoB levels and ApoB/ApoA ratio) and adiponectin levels in women, while in men significant interactions only affected ApoA levels. Secondly, significant interactions affecting plasma lipid parameters were observed mostly with total dietary CHO%, complex CHO% (provided mainly by starches) and dietary fat%. No significant interactions were observed with total dietary PUFA%, and unfortunately ALA, LA or Ω-6/Ω-3 intake was not quantified in this cohort. It is also noteworthy that the only significant interaction of rs174616 with macronutrients in the GRE-PUFA trial was observed for total dietary carbohydrate, affecting erythrocyte membrane Δ6Des activity. To our knowledge, interactions of dietary carbohydrate with FADS cluster variation have not been previously reported in humans, so the results should be interpreted with caution and need replication in independent studies.

Although FADS gene variation interaction with dietary carbohydrate has not been reported in humans, there is experimental evidence supporting an effect of dietary carbohydrate on desaturase expression and enzyme activities, in line with the interactions found in the present study. It is known that mRNA expression and activity of desaturase enzymes are influenced by numerous dietary components, including simple and complex carbohydrates [76]. In murine models, a high carbohydrate diet increased hepatic *Fads2* mRNA expression and Δ6Des activity decreasing Δ5Des activity [77]. Results from an independent study in mice also suggested that hepatic Δ6D activity was increased with a high-carbohydrate diet composed of a mixture of starch and sucrose [78]. The mechanisms explaining how a high-carbohydrate diet affects desaturation pathway activity are not fully understood, and further comparative investigations of the effects of different dietary carbohydrates on LC-PUFA synthesis are warranted.

4.4. The relationship of DGLA levels and LC-PUFA-associated health indicators with HOMA-IR and body fat % differs according to rs174616 genotype

Overall, it is known that Ω-3 index, EPA and DHA serum or tissue membrane levels correlate with a better cardiometabolic profile, while AA/EPA and Ω-6/Ω-3 ratios, and more recently DGLA levels correlate with a less favorable cardiometabolic profile [79,80]. However, it has been noted that the associations of DGLA and other Ω −6 PUFAs with HOMA-IR differ according to ethnicity [81]. In the present study, we observed that these correlations were inverse in individuals with the ancestral "CC" genotype, particularly affecting the correlation of these indices with HOMA-IR (statistically significant interactions between genotype and Δ5Des activity, DGLA levels, Ω-3 index, EPA and DHA levels, AA/EPA and Ω-6/Ω-3 ratios). Correlations of five of these LC-PUFA measurements (Ω-3 index, EPA and DHA levels, AA/EPA and Ω-6/Ω-3 ratios) with body fat percentage (BF%) were also inverse in individuals with the "CC" genotype, showing statistically significant interactions. To our knowledge, only one previous study reported a significant interaction between DGLA and rs174575 genotype (LDB1) affecting HOMA-IR in Koreans [82]. Altogether, these data support a role for FADS gene cluster SNPs in these correlations, which should be confirmed and clarified in further studies.

4.5. Study limitations

Several limitations of our study should be pointed out. Firstly, F_{st} and PBS are allele frequency-based tests, which are indirect measures of selection. However, our results are consistent with those of many studies that have identified different selection signals within the FADS gene cluster in many populations in different continents [9,22–26,54]. Secondly, FFQs are not always reproducible, but are a widely used tool to assess diet. In this regard, a recent meta-analysis suggests that validated FFQs are suitable to assess the overall dietary intake in nutritional epidemiological studies [83]. While we used a FFQ validated in the Mexican population, our results should be interpreted with caution and need to be replicated in independent studies, and in larger cohorts. Finally, because association does not imply causation, further studies are required to clearly establish the relationship between dietary carbohydrate intake, rs174616 genotype and cardiometabolic parameters.

5. Conclusions

We identified a potential signal of positive selection (*FADS2* variant rs174616) in a linkage disequilibrium block independent of other previously identified *FADS* gene cluster selection signals. Although it has been previously stated that variants within this independent block are not clearly associated with clinical traits, we show evidence that this signal is associated with both cardiometabolic and Ω-6 and Ω-3 PUFA parameters in the Mexican population, and that the most significant gene-diet interactions observed involved total dietary carbohydrate and complex carbohydrate percentages. Finally, the associations of DGLA and other Ω-6/Ω-3 PUFA clinical indicators with HOMA-IR differed according to the rs174616 genotype, which has implications affecting how these clinical indicators should be interpreted.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Maria Elizabeth Tejero reports financial support was provided by Nestec Ltd. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35477.

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