Serum Lipid Concentrations and FADS Genetic Variants in Young Mexican College Students: The UP-AMIGOS Cohort Study

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Abstract

Background: Recent genome-wide association studies in the Mexican population have identified several genetic loci associated with blood lipid levels in adults. However, studies focusing on the fatty acid desaturase (FADS) gene cluster have been understudied in this population, even though it seems associated with lipid profiles in other ethnicities. The aim of this study was to test associations between single nucleotide polymorphisms (SNPs) in the FADS cluster (rs174546, rs1535, rs174548, rs174550, rs174450, and rs174618) and serum lipid profiles in young Mexicans. Methods: Anthropometrics, serum lipid profiles, and FADS SNPs were measured in 998 subjects in the UP-AMIGOS cohort study. Genotype-phenotype (total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and very-low-density lipoprotein [VLDL]) associations were assessed using PLINK adjusted for sex, age, and body mass index (BMI). Results: Among 6 FADS SNPs, we found that carriers of the C-allele of the FADS1-rs174546 showed a significant association with lower TG concentrations (β = –12.6 mg/dL, p = 0.009) and lower VLDL concentrations (β = –2.52 mg/dL, p = 0.005). We found that rs174546, rs1535, and rs174550 were in high linkage disequilibrium (r² > 0.80). There were no significant associations between rs174550, rs174548, and rs174618 and lipid profiles. Conclusion: A genetic variant in the FADS1 (rs174546) gene is a major contributor of plasma TG and VLDL concentrations in healthy young Mexicans.

Introduction

In Mexico, 65% of the adult population has low high-density lipoprotein cholesterol (HDL-C ≤ 40 mg/dL) and 43.6% is hypercholesterolemic (total cholesterol [TC] ≥ 200

Keywords

FADS genotype · Blood lipid · Young healthy Mexicans
mg/dL); in particular low HDL-C and high TC increase the risk for cardiovascular disease (CVD) [1]. Similar patterns have been found among young Mexicans aged 20–29 years, with 62% having low HDL-C (<40 mg/dL) and 22% having high levels of triglycerides (TG ≥150 mg/dL), two clinical markers of metabolic syndrome and risk factors for CVD [1]. Moreover, the prevalence of obesity has rapidly increased among the younger population during the last decade [2, 3]. In European populations, over 157 loci associated with either low HDL-C, high low-density lipoprotein cholesterol (LDL-C), high TG, or high TC have been identified in those genetically predisposed to the development of dyslipidemia [4–6]. Additional loci were identified in Mexican adults with a combined family history of hyperlipidemia and hypertriglyceridemia, further implicating the role of genetic variation in this at-risk population [7, 8].

The FADS gene cluster includes 3 genes: FADS1, FADS2, and FADS3 [9]. The FADS gene cluster is involved in the elongation and formation of long-chain fatty acids from both dietary and endogenous precursors, and thus its role in plasma fatty acid concentration is essential [9]. Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) in FADS1 and FADS2 to be associated with adverse lipid profiles [4–6, 10–12]. Additional studies continue to confirm these associations in both adults and children of European descent [13–17]. Over 80% of genetic association research to date has been conducted in populations of European descent, despite strong evidence that genetic associations are not identical across ethnic groups [18, 19]. A single case/control study conducted in Mexican adults identified FADS3 as a causal gene for familial combined hyperlipidemia and elevated TG, but variants in other genes of this cluster (FADS1/FADS2) and associations with blood lipids have not been studied in healthy young Mexicans who may be at risk for the development of dyslipidemia due to genetic predisposition [20]. Therefore, the aim of this study was to establish associations between 6 variants in the FADS gene cluster (rs174546, rs1535, rs174548, rs174550, rs174450, and rs174618) and serum lipid profiles in young Mexicans in the UP-AMIGOS cohort study [21, 22].

Material and Methods

Study Population

The UP-AMIGOS cohort study (Universities of San Luis Potosi and Illinois: A Multidisciplinary Investigation on Genetics, Obesity, and Social Environment) is a cross-sectional study of young adult applicants from the Autonomous University of San Luis Potosi (Universidad Autónoma de San Luis Potosí, UASLP for its acronym in Spanish). Briefly, a total of 10,000 samples and validated self-administered food frequency questionnaires (FFQ) for the Mexican population were collected from volunteers in 2009 at the UASLP in Mexico [23]. A detailed description of the data collection and phenotypes of the subjects participating in the UP-AMIGOS cohort study has been published previously [20, 21]. As previously described [21, 22], >10,000 individuals were recruited and screened for this multidisciplinary investigation, and only 998 were found eligible on the basis of the selection criteria with completed demographics, lipid profiles, and genetic data. Dietary intakes were only available for a subset of 642 of 998 participants. According to the methodology for analysis of dietary data from the Mexican National Health and Nutrition Survey 2006 (Ensanut 2006 for its acronym in Spanish), unreliable dietary intake data are defined as reporting consumption of <500 kcal per day, or reporting a very high caloric intake, 5 standard deviations above the mean [23, 24]. Thus, a subset of 581 participants (61 participants were excluded) were found with reliable data to analyze gene-diet interactions. Written informed consent was obtained for all participants. Institutional Review Boards of both the UASLP and the University of Illinois at Urbana-Champaign approved the study protocol.

Biochemical Measurements

Serum TC, HDL-C, and TG were determined after overnight fast by standard methods at the Clinical Research Laboratory of the Chemistry School at the UASLP in Mexico. LDL-C and very-low-density lipoprotein cholesterol (VLDL-C) were calculated using the Friedewald equation [25]. Hypertriglyceridemia was defined as a TG concentration ≥150 mg/dL, hypercholesterolemia as TC ≥200 mg/dL, high LDL-C as a concentration >130 mg/dL, and low HDL-C as ≤40 mg/dL in males and ≤50 mg/dL in females [26].

DNA Extraction, SNP Selection, and Genotyping

Blood was collected in EDTA tubes, stored at −80 °C at the Clinical Research Laboratory of the Chemistry School at the UASLP in Mexico, and then transported to the Terán-García Laboratory at the University of Illinois Urbana-Champaign in the USA for genotyping. DNA was extracted using Puregene reagents (Gentra Puregene Blood Kits, QIAGEN, Valencia, CA, USA) and stored at −20 °C. Detailed DNA extraction and genotype determination methods had previously been described [27]. Six FADS SNPs (rs174546, rs1535, rs174548, rs174550, rs174450, and rs174618) were selected for analysis based on previously published evidence of their associations with serum lipid profiles [10–17].

Dietary Fatty Acid Intake

Nutritional data were available for the analysis of 581 of the 998 participants. Dietary intakes of total fat, saturated fat, monounsaturated fat, and polyunsaturated fat were extracted from the FFQ. Dietary intake of omega-3 was calculated from the sum of daily eicosapentaenoic acid (EPA; 20:5 n-3), docosapentaenoic acid (22:5 n-3), and docosahexaenoic acid (DHA; 22:6 n-3), and for omega-6 from the sum of linoleic acid (LA; 18:2 n-6), γ-linolenic acid (18:3 n-6), and arachidonic acid (AA; 20:4 n-6). Dietary intakes are reported as intakes in grams per day and as the percentage contribution to the total energy intake (%E), and were analyzed using standard methodologies published by the Ensanut 2006 [23, 24].
Statistical Analysis

Results are reported as means ± standard errors of the mean. All the analyses were performed using PLINK software [28]. Continuous variables were examined for normality, and non-normal variables (TG and VLDL-C) were log-10 transformed for significance testing. Linkage disequilibrium (LD) was used to analyze the correlation ($r^2$) between FADS SNPs. General linear regression models adjusted for sex, age, and body mass index (BMI) were used to test associations between FADS SNPs and blood lipid concentrations (TC, TG, HDL-C, LDL-C, and VLDL) assuming an additive model, and adjusted for multiple comparisons using the Bonferroni correction. For all tests, the Bonferroni correction was set at $\alpha/n$, where $\alpha = 0.05$ and $n = 3$, and therefore significant $p$ was <0.016. All reported $p$ values were 2-tailed, and statistical significance was defined at $\alpha = 0.05$ level. Participants with missing information on serum lipid concentrations and/or genotypes were excluded from the analyses involving a particular SNP (data can be found in Table 3). Moreover, in a subset of 581 subjects with completed FFQ data, gene-nutrient interactions were tested for FASD1-rs174546.

Results

Characteristics of the Study Population

Characteristics of the participants are summarized in Table 1. BMI, TG, HDL-C, and VLDL-C were significantly different between males and females ($p < 0.01$). In males, levels of TG and VLDL-C were higher, whereas HDL-C was lower compared to females (Table 1). Overall, 37% of the sample met diagnostic criteria for low HDL-C ($\leq 40$ mg/dL in males and $\leq 50$ mg/dL in females), 16% for hypercholesterolemia (TC $\geq 200$ mg/dL), 15% for hypertriglyceridemia (TG $\geq 150$ mg/dL), and 9% for high LDL-C (LDL > 130 mg/dL). Finally, we found that 34% of the participants had a BMI $\geq 25$, with 23% being overweight and 11% being obese.

FADS Single Nucleotide Polymorphisms

The genotype and allele frequency of the 6 FADS SNPs in this analysis are shown in Table 2. We found 3 FADS
SNPs in high LD with each other. \textit{FADS1-rs174546} and \textit{FADS2-rs1535} were in strong LD ($r^2 = 0.89$) and belong to the same block. \textit{FADS1-rs174546} was in high LD with \textit{rs174550} ($r^2 = 0.80$), and \textit{FADS1-rs174550} was in high LD with \textit{rs174548} ($r^2 = 0.81$). Hence, we included 3 \textit{FADS} SNPs (\textit{rs174546}, \textit{rs174618}, and \textit{rs174450}) for further analysis.

\textit{Frequency Distribution of FADS1-rs174546 among Populations}

Striking differences were observed in the allele frequencies across several populations (Fig. 1). In the UP-AMIGOS cohort study, the T-allele was the major allele which replicates the allele frequencies reported by the 1000 Genomes Browser for the Mexican population [29]. Thus, only 5 (Vietnam, Peru, and China) out of 26 populations included in the 1000 Genomes Browser project had the C-allele as the minor allele, including Mexicans (the overall minor allele frequency [MAF] was 30% TT genotypes) (Fig. 1).

\textit{Associations between FADS SNPs, Dietary Intakes and Blood Lipid Concentrations}

Means of blood lipid concentrations according to \textit{FADS} genotype are presented in Table 3. Homozygous carriers of the minor C-allele of \textit{FADS1-rs174546} were
Table 3. Blood lipid concentrations by FADS genotypes in the UP-AMIGOS study

| SNPs  | n   | MM      | Mm      | mm      | β      | p value |
|-------|-----|---------|---------|---------|--------|---------|
| TC    |     |         |         |         |        |         |
| rs174546 | 816 | 153.4±60.5 | 151.1±67.9 | 127.6±74.0 | -8.03  | 0.03    |
| rs174548 | 836 | 144.3±69.4 | 149.4±64.5 | 121.7±80.4 | -3.50  | 0.34    |
| rs174618 | 841 | 144.1±69.8 | 145.8±66.7 | 141.3±71.1 | 0.74   | 0.74    |
| TG    |     |         |         |         |        |         |
| rs174546 | 817 | 107.3±70.9 | 95.8±62.7 | 78.3±50.5  | -12.6  | 0.009*  |
| rs174548 | 837 | 100.5±71.9 | 97.8±65.4 | 72.1±50.2  | -7.96  | 0.27    |
| rs174618 | 842 | 96.6±66.2  | 100.2±72.5 | 82.6±52.8  | -1.17  | 0.95    |
| HDL-C |     |         |         |         |        |         |
| rs174546 | 817 | 44.0±19.0 | 42.7±21.1 | 39.7±21.3  | -1.92  | 0.08    |
| rs174548 | 837 | 41.3±23.0 | 41.3±21.5 | 35.0±24.3  | -2.20  | 0.12    |
| rs174618 | 842 | 40.0±22.5 | 41.1±21.8 | 44.7±26.1  | 1.74   | 0.15    |
| LDL-C |     |         |         |         |        |         |
| rs174546 | 817 | 86.2±40.9 | 86.6±46.1 | 74.5±47.5  | -2.88  | 0.23    |
| rs174548 | 841 | 78.7±46.0 | 82.4±46.3 | 69.1±53.3  | -0.45  | 0.86    |
| rs174618 | 842 | 76.7±47.8 | 80.5±46.7 | 80.2±46.5  | 1.82   | 0.47    |
| VLDL  |     |         |         |         |        |         |
| rs174546 | 817 | 21.5±14.2 | 19.2±12.5 | 15.7±10.1  | -2.52  | 0.005*  |
| rs174548 | 837 | 20.1±14.4 | 19.6±13.1 | 14.4±10.0  | -2.24  | 0.18    |
| rs174618 | 842 | 19.3±13.2 | 20.0±14.5 | 16.5±10.6  | -0.32  | 0.87    |

Data are expressed as means ± standard deviation (in mg/dL). p values were adjusted by age, sex, and body mass index. TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein cholesterol. * Significant p value of log-10 transformed data adjusted after Bonferroni correction.

Table 4. Dietary intakes stratified by FADS1-rs174546 genotypes in the UP-AMIGOS study

| Dietary intake | n   | TT (MM) | CT (Mm) | CC (mm) | p value |
|----------------|-----|---------|---------|---------|---------|
| Energy, kcal   | 581 | 2,287±1,131 | 2,307±1,065 | 2,619±1,581 | 0.23    |
| TFA, g/day     | 581 | 90.7±52.1  | 92.5±46.1 | 108.4±69.4 | 0.20    |
| SFA, g/day     | 581 | 28.9±17.8  | 28.6±14.3 | 36.5±25.2  | 0.08    |
| MUFA, g/day    | 581 | 35.2±21.8  | 35.2±18.4 | 41.8±26.3  | 0.31    |
| PUFA, g/day    | 581 | 17.5±12.8  | 18.1±11.9 | 20.6±16.3  | 0.41    |
| Omega-3, g/day | 581 | 1.3±0.9    | 1.3±1.2   | 1.3±1.1    | 0.33    |
| Omega-6, g/day | 581 | 9.5±7.0    | 9.7±6.3   | 10.4±6.8   | 0.89    |
| TFA, %E        | 581 | 35.2±7.7   | 36.4±7.6  | 37.3±6.7   | 0.14    |
| SFA, %E        | 581 | 11.2±2.9   | 11.3±2.8  | 12.3±2.6   | 0.26    |
| MUFA, %E       | 581 | 13.5±3.6   | 13.8±3.5  | 14.5±2.9   | 0.06    |
| PUFA, %E       | 581 | 6.9±3.2    | 7.0±3.0   | 7.0±2.7   | 0.81    |
| Omega-3, %E    | 581 | 0.5±0.3    | 0.5±0.3   | 0.5±0.2    | 0.78    |
| Omega-6, %E    | 581 | 6.7±1.5    | 3.8±1.8   | 3.7±1.4   | 0.16    |

Data are expressed as means ± standard deviation in grams per day or percentage of energy (%E) from calories. p values were adjusted by age, sex, and body mass index for gene-nutrient interaction. Dietary intake of omega-3 was calculated from the sum of daily eicosapentaeenoic acid (20:5 n-3), docosapentaeenoic acid (22:5 n-3), and docosahexaenoic acid (22:6 n-3), and for omega-6 from the sum of linoleic acid (18:2 n-6), γ-linolenic acid (18:3 n-6), and arachidonic acid (20:4 n-6). TFA, total fat; SFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; MM, major; mm, minor.
strongly associated with lower TG ($\beta = -12.6$ mg/dL, $p = 0.009$) and lower VLDL ($\beta = -2.52$ mg/dL, $p = 0.005$) concentrations compared to carriers of the T-allele. Table 4 shows total dietary intakes stratified by FADS1-rs174546. There were no significant differences in dietary intakes across FADS1-rs174546 genotypes. Moreover, no significant interaction effects were observed between dietary intakes and FADS1-rs174546 genotypes on blood cholesterol concentrations (data not shown).

**Discussion**

In this cross-sectional analysis, we found that the minor C-allele of FADS1-rs174546 was associated with lower plasma TG and VLDL concentrations in this cohort of young Mexican adults. To our knowledge, this is the first study to assess plasma lipid profiles and FADS genotype in healthy young Mexican adults. A study conducted in older Mexican adults diagnosed with familial hypercholesterolemia found FADS3-rs174547 to be strongly associated with high TG levels [20]. Evidence indicated that FADS1-rs174546 and FADS3-rs174547 are in strong LD [29].

MAF varies by population, and even though the C-allele of FADS1-rs174546 is minor in the Mexican population, it is not in other populations [29]. Two independent studies in diverse populations have confirmed these dramatic differences in the allele frequencies of variants in the FADS gene cluster across populations [19, 30].

Numerous studies have reported a significant association between FADS variants and lower TC, LDL-C, HDL-C, and higher TG concentrations in the European population [13–17]. Despite the population MAF found in our study, the T-allele of FADS1-rs174546 was associated with increased TG concentrations, and replicates previous associations in diverse populations, such as the association of higher TG concentrations among carriers of the minor T-allele of FADS1-rs174546 (CT + TT genotype) in French Canadians [31]. On the other hand, our results did not replicate previous associations between the minor T-allele in the FADS1-rs174546 and lower TC, non-HDL-C, and HDL-C concentrations [14–16]. Nevertheless, our study confirms the marked differences between populations regarding MAF in the FADS gene cluster, and replicates the effect of FADS1-rs174546 on TG concentrations previously reported by others [7, 8, 31]. In East Asian subpopulations, the C-allele of FADS1-rs174547 (in LD with rs174546) has been associated with lipid dysregulation, but these associations are not identical between ethnic subgroups [32]. This study found that in the Japanese population, the C-allele of FADS1-rs174547 was associated with increased TG and lower HDL-C concentrations, but in the Mongolian population it was associated with lower LDL-C concentrations [32]. Similar associations were reported in the Northern and Southern Chinese populations; the C-allele of rs174550 was associated with high TC levels in Beijing participants, but this allele was associated with lower HDL-C in Shanghai residents [33]. A possible explanation for the variability in lipid-gene associations could be due to differences in dietary fat intake between these two populations [19, 32, 33]. Moreover, the different LD patterns across populations may explain the different associations found in lipid traits [19, 30].

The role of dietary fat intake, specifically long-chain polyunsaturated fatty acids (LCPUFA), on lipid profiles modified by genetic variation has been well studied [17, 34, 35]. Briefly, the FADS1/FADS2 gene encodes two enzymes (delta-5 [D5D] and delta-6 [D6D]) responsible for the double bond formation of LCPUFA through desaturation and elongation of essential fatty acids (EFA) such as α-linolenic acid (ALA) and LA [9]. The amount of substrates (ALA and LA) derived from the diet is equivalent to the fatty acid composition in the body [36]. The activities of D5D and D6D, encoded by FADS1 and FADS2, respectively, can be modulated by diet [9, 36, 37]. Variants in the FADS gene cluster that result in a decreased transcription of key enzymes in these pathways may result in decreased efficiency of these enzymes to convert EFA to LCPUFA [9, 16, 37, 38]. A large family-based study of the genetics of coronary artery disease in Mexican Americans (San Antonio Family Heart Study) found that FADS1/FADS2 SNPs have a significant influence on the variation in estimated plasma and erythrocyte D5D activities. D5D is a rate-limiting enzyme involved in the conversion of EFA to AA (20:4 ω–6) and EPA (20:5 ω–3) [39]. This study also found that D5D and D6D activities were highly heritable, with a strong linkage (LD) to chromosome 11 for estimated erythrocyte D5D activity [39]. Thus, minor alleles of FADS1 and FADS2 SNPs were associated with higher D5D activity, which results in an increased plasma and erythrocyte AA, and reduced EPA levels [39]. Hence, individuals with these variants may then possibly benefit from dietary increases in LCPUFA. In contrast, in the European population, minor alleles in FADS1 and FADS2 genes were associated with higher ALA and LA levels, and lower AA and EPA levels [19, 36, 37]. In this manner, higher D5D activity has also been associated with lower LDL-C and TG, and higher HDL-C

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concentrations, which play an important role in the prevention of atherosclerosis and CVD [17, 40]. These differences in desaturase activities may be related to differences in the genetic background and dietary patterns across populations [31–36]. These associations have been demonstrated in cross-sectional analyses and feeding interventions, but not in Mexican populations [15, 16, 31–38]. Currently, dietary intakes of EFA (ALA, LA), the FADS enzyme substrates, and LCPUFA are low in the Mexican population [41], and thus carriers of the T-allele of FADS1-rs174546 may be at an even greater disadvantage if they do not meet dietary recommendations. Furthermore, a meta-analysis for dyslipidemias found that a high intake of unsaturated fat relative to saturated fat reduces TC levels by 10.68 mg/dL, as LCPUFAs serve as key transcription regulators in genes related to de novo lipogenesis [42, 43]. A high intake of unsaturated fat, especially LA, is associated with a decreased risk of CVD and coronary heart events, despite the role of these compounds in pro-inflammatory signaling pathways [44].

Several limitations of our study should be addressed. First, no data were available regarding lifestyle factors, such as medication use, smoking habits, alcohol consumption, or physical activity for our population. Second, such as medication use, smoking habits, alcohol consumption, or physical activity for our population. Second, first, no data were available regarding lifestyle factors, such as medication use, smoking habits, alcohol consumption, or physical activity for our population. Second, this study is a self-administered questionnaire with multidisciplinary outcomes; therefore, a high intake of unsaturated fat relative to saturated fat reduces TC levels by 10.68 mg/dL, as LCPUFAs serve as key transcription regulators in genes related to de novo lipogenesis [42, 43]. A high intake of unsaturated fat, especially LA, is associated with a decreased risk of CVD and coronary heart events, despite the role of these compounds in pro-inflammatory signaling pathways [44].

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Disclosure Statement

The authors declare no conflicts of interest.

References

1 Aguilar-Salinas CA, Gomez-Perez FJ, Rull J, Villalpando S, Barquera S, Rojas R: Prevalence of dyslipidemias in the Mexican National Health and Nutrition Survey 2006. Salud Publica Mex 2010;52(suppl 1):544–553.

2 Denova-Gutierrez E, Jimenez-Aguilar A, Halley-Castillo E, Huitron-Bravo G, Talavera JO, Pineda-Perez D, Diaz-Montiel JC, Salmeron J: Association between sweetened beverage consumption and body mass index, proportion of body fat and body fat distribution in Mexican adolescents. Ann Nutr Metab 2008;53:245–251.

3 Denova-Gutierrez E, Talavera JO, Huitron-Bravo G, Mendez-Hernandez P, Salmeron J: Sweetened beverage consumption and increased risk of metabolic syndrome in Mexican adults. Public Health Nutr 2010;13:835–842.

4 Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al: Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010;466:707–713.

5 Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al: Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;45:1274–1283.

6 Johansen CT, Kathiresan S, Hegele RA: Genetic determinants of plasma triglycerides. J Lipid Res 2011;52:189–206.
Weissglas-Volkov D, Aguilar-Salinas CA, Nikkola E, Deere KA, Cruz-Bautista I, Arellano-Campos O, Munoz-Hernandez LL, Gomez-Munguia L, Ordonez-Sanchez ML, Reddy PM, Luis A, Matikainen N, Taskinen MR, Riba I, Cantor RM, Sinhjem JS, Tusie-Luna T, Pajukanta P: Genomic study in Mexicans identifies a new locus for triglycerides and refines European lipid loci. J Med Genet 2013;50:298–308.

8 Weissglas-Volkov D, Aguilar-Salinas CA, Sinhjem JS, Riba I, Huertas-Vazquez A, Ordonez-Sanchez ML, Rodriguez-Guillen R, Cantor RM, Tusie-Luna T, Pajukanta P: Investigation of variants identified in Caucasian genome-wide association studies for plasma high-density lipoprotein cholesterol and triglycerides levels in Mexican dyslipidemic study samples. Circ Cardiovasc Genet 2010;3:31–38.

9 Nakamura MT, Nara TY: Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. Annu Rev Nutr 2004;24:345–376.

10 Kithiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, et al: Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet 2009;41:56–65.

11 Aulchenko YS, Ripatti S, Lindqvist I, Boomsma D, Heid IM, Pramstaller PP, et al: Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. Nat Genet 2009;41:47–55.

12 Sabatti C, Service SK, Hartikainen AL, Pouta A, Ripatti S, Brodsky J, et al: Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. Nat Genet 2009;41:35–46.

13 Standl M, Lattka E, Stach B, Koletzko S, Bauer CP, von Berg A, Berdel D, Kramer U, Schaaf B, Roder S, Herbarth O, Buyken A, Drogies T, Thiery J, Koletzko B, Heinrich J; GINIplus Study Group, LIASplus Study Group: FADS1 FADS2 gene cluster, PUFA intake and blood lipids in children: results from the GINIplus and LIASplus studies. PLoS One 2012;7:e3780.

14 Molto-Puigmarti C, Jansen E, Heinrich J, Standl M, Mensink RP, Plat J, Penders J, Mommers M, Koppelman GH, Postma DS, Thijs C: Genetic variation in FADS genes and plasma cholesterol levels in 2-year-old infants: KOALA Birth Cohort Study. PLoS One 2013;8:e61671.

15 Dumont J, Huybrechts I, Spinneker A, Gottrand F, Grammatikaki E, Bevilacqua N, Vyncke K, Widholm K, Kawasaki A, Mohar D, Labayen I, Gonzalez-Gross M, Amouyel P, Moreno LA, Meirhaeghe A, Dallongeville J; HELENA Study Group: FADS1 genetic variability interacts with dietary alpha-linolenic acid intake to affect serum non-HDL-cholesterol concentrations in European adolescents. J Nutr 2011;141:1247–1253.

16 Lu Y, Feskens EJ, Dolle ME, Imholz S, Vermeulen WM, Muller M, Boer JM: Dietary n-3 and n-6 polyunsaturated fatty acid intake interacts with FADS1 genetic variation to affect total and HDL-cholesterol concentrations in the Doetinchem Cohort Study. Am J Clin Nutr 2010;92:258–265.

17 Hellsland S, Sonesedd E, Ericson U, Gullberg B, Wirfléit E, Hedblad B, Orho-Melander M: Intake levels of dietary long-chain PUFA:s modify the association between genetic variation in FADS and LDL-C. J Lipid Res 2012;53:1183–1189.

18 Bustamante CD, De La Vega FM, Burchard EG: Genomics for the world. Nature 2011;475:163–165.

19 Ameer A, Enroth S, Johansson A, Zaboli G, Igl W, Johansson AC, Rivas MA, Daly MJ, Schmitz G, Hicks AA, Meitinger T, Feuk L, van Duijn C, Oostra B, Pramstaller PP, Rudan I, Wright AF, Wilson JF, Campbell H, Gylensten U: Genetic adaptation of fatty-acid metabolism: a human-specific haplotype increasing the biosynthesis of long-chain omega-3 and omega-6 fatty acids. Am J Hum Genet 2012;90:809–820.

20 Plaisier CL, Horvath S, Huertas-Vazquez A, Thiery J, Koletzko B, Herrera MF, Tusie-Luna T, Aguilar-Salinas C, Pajukanta P: A systems genetics approach implicates USF1, FADS3, and other causal candidate genes for familial combined hyperlipidemia. PLoS Genet 2009;5:e1000642.

21 Andrade FC, Vazquez-Vidal I, Flood T, Ardillias-Carrillo C, Vargas-Morales JM, Medina-Cerda E, Teran-Garcia M: One-year follow-up changes in weight are associated with changes in blood pressure in young Mexican adults. Public Health 2012;126:535–540.

22 Mosley MA, Andrade FCD, Aradillas-Garcia MA, Vazquez-Vidal I, Ferrandez-Bautista I, Herrera MF, Tusie-Luna T, Aguilar-Salinas C, Pajukanta P: A systems genetics approach implicates USF1, FADS3, and other causal candidate genes for familial combined hyperlipidemia. PLoS Genet 2009;5:e1000642.

23 Rodriguez-Ramirez S, Mundo-Rosas V, Jimenez-Aguilar A, Shamah-Levy T: Consumption of dairy and metabolic syndrome risk in a convenient dietary patterns in an adult Mexican population. Salud Publica Mex 2016;58:2325–2333.

24 Denova-Gutierrez E, Tucker KL, Salmeron J, Flores M, Barquera S: Relative validity of a food frequency questionnaire to identify dietary patterns in an adult Mexican population. Salud Publica Mex 2016;58:608–616.

25 Friedewald WT, Levy RB, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

26 Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunerber G, Guerin CK, Bell DS, Mechanick JJ: American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23:1–87.

27 Toran-Garcia M, Vazquez-Vidal I, Andrade FC, Mosley M, Medina-Cerda E, Aradillas-Garcia C: FTO genotype is associated with body mass index and waist circumference in Mexican young adults. OGJ Gen 2013;3:344.

28 Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC: PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–575.

29 1000 Genomes Browser, version 3.7. Updated September 2016. https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/

30 Mathias RA, Fu W, Akey JM, Ainsworth HC, Torgerson DG, Rucinski I, Sergeant S, Barnes KC, Chilton FH: Adaptive evolution of the FADS gene cluster within Africa. PLoS One 2012;7:e4926.

31 Cormier H, Rucklova K, Paradis A-M, Thifault E, Garneau V, Lemieux S, Couture P, Vohl M-C: Association between polymorphisms in the fatty acid desaturase gene cluster and the plasma triacylglycerol response to an n-3 PUFAs supplementation. Nutrients 2012;4:1026–1041.

32 Nakayama K, Bayasgalar T, Tazoe F, Yanagi-sawa Y, Gotoh T, Yamanaka K, Ogawa A, Munkhtulga L, Chimedregue U, Kagaya Y, Ishibashi S, Iwamoto S: A single nucleotide polymorphism in the FADS1/FADS2 gene is associated with plasma lipid profiles in two genetically similar Asian ethnic groups with distinctive differences in lifestyle. Hum Genet 2010;127:685–690.

33 Zhu J, Sun Q, Zong G, Si Y, Liu C, Qi Y, Ye X, Sun L, Sheng H, Li H, Lin X: Interaction between a common variant in FADS1 and erythrocyte polyunsaturated fatty acids on lipid profile in Chinese Hans. J Lipid Res 2013;54:1477–1483.

34 Bokor S, Dumont J, Spinneker A, Gonzalez-Gross M, Nova E, Widholm K, Moschonis G, Stehle P, Amouyel P, De Henauw S, Molnar D, Moreno LA, Meirhaeghe A, Dallongeville J: Single nucleotide polymorphisms in the FADS gene cluster are associated with delta-5 and delta-6 desaturase activities estimated by serum fatty acid ratios. J Lipid Res 2010;51:2325–2333.

35 Zhou L, Nilsson A: Sources of eicosanoid precursor fatty acid pools in tissues. J Lipid Res 2001;42:1521–1542.

36 Martinelli N, Consoli I, Olivieri O: A “desaturase hypothesis” for atherosclerosis: Janus-faced enzymes in omega-6 and omega-3 polyunsaturated fatty acid metabolism. J Nutrigenet Nutrigenomics 2009;2:129–139.
37 Gillingham LG, Harding SV, Rideout TC, Yurkova N, Cunnane SC, Eck PK, Jones PJ: Dietary oils and FADS1-FADS2 genetic variants modulate \([^{13}C]\)alpha-linolenic acid metabolism and plasma fatty acid composition. Am J Clin Nutr 2013;97:195–207.

38 Roke K, Mutch DM: The role of FADS1/2 polymorphisms on cardiometabolic markers and fatty acid profiles in young adults consuming fish oil supplements. Nutrients 2014;6:2290–2304.

39 Voruganti VS, Higgins PB, Ebbesson SO, Kennish J, Goring HH, Haack K, Laston S, Drigalenko E, Wenger CR, Harris WS, Fabsitz RR, Devereux RB, Maccluer JW, Curran JE, Carless MA, Johnson MP, Moses EK, Blangero J, Umans JG, Howard BV, Cole SA, Comuzzie AG: Variants in CPT1A, FADS1, and FADS2 are associated with higher levels of estimated plasma and erythrocyte delta-5 desaturases in Alaskan Eskimos. Front Genet 2012;3:86.

40 Daneshmand R, Kurl S, Tuomainen TP, Virtanen JK: Associations of estimated Delta-5-desaturase and Delta-6-desaturase activities with stroke risk factors and risk of stroke: the Kuopio Ischaemic Heart Disease Risk Factor Study. Br J Nutr 2017;117:582–590.

41 Ramírez-Silva I, Villalpando S, Moreno-Sarácho JE, Bernal-Medina D: Fatty acids intake in the Mexican population. Results of the National Nutrition Survey 2006. Nutr Metab 2011;8:33.

42 Hannon BA, Thompson SV, An R, Teran-Garcia M: Clinical outcomes of dietary replacement of saturated fatty acids with unsaturated fat sources in adults with overweight and obesity: a systematic review and meta-analysis of randomized control trials. Ann Nutr Metab 2017;71:107–117.

43 Fernandez ML, West KL: Mechanisms by which dietary fatty acids modulate plasma lipids. J Nutr 2005;135:2073–2078.

44 Wang DD, Hu FB: Dietary fat and risk of cardiovascular disease: recent controversies and advances. Annu Rev Nutr 2017;37:423–446.