RESEARCH ARTICLE

Polymorphisms in the SCD1 gene are associated with indices of stearoyl CoA desaturase activity and obesity: A prospective study

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Scope: The serum fatty acid (FA) composition is influenced by dietary fat and the endogenous production of FAs. Stearoyl CoA desaturase 1 (SCD1) is the rate-limiting enzyme catalyzing the synthesis of MUFAs from saturated FAs. Variations in SCD1 activity have been associated with obesity, diabetes, or inflammation. We evaluated the associations between genetic variation of the SCD1 gene, SCD1 activity, intake of oil, and obesity in a population-based prospective study in southern Spain.

Methods and results: We collected phenotypic, metabolic, nutritional, and genetic information. The type of dietary fat was assessed from samples of cooking oil taken from the participants' kitchens and analyzed by GC. A total of nine single nucleotide polymorphisms (SNPs) of the SCD1 gene were analyzed by SNPlex technology. We found a significant association between SCD1 genetic variation and enzyme activity in four of nine polymorphisms studied. An interaction between rs10883463 and olive oil intake on the [18:1/18:0] desaturase index was found ($p = 0.009$). We also showed that genetic variations in the SCD1 gene were associated with obesity.

Conclusion: Our results show a relationship between genetic variation of the SCD1 gene, enzyme activity, and the risk of obesity, an association that is not independent of the type of oil consumed.

Keywords:
Obesity / Olive oil / Polymorphisms / Prospective study / Stearoyl CoA desaturase

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1 Introduction

Abnormalities in lipid metabolism cause obesity and insulin resistance, leading to metabolic diseases such as type 2 diabetes [1]. The serum fatty acid (FA) composition is influenced by dietary fat and the endogenous production of FAs. Stearoyl CoA desaturase-1 (SCD1) is the rate-limiting enzyme catalyzing the synthesis of MUFAs, mainly oleate (18:1) and palmitoleate (16:1) [2]. MUFAs are the main substrates for synthesis of triglycerides, cholesterol esters, wax esters,

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Abbreviations: CI, confidence interval; **FA**, fatty acids; **HWE**, Hardy–Weinberg equilibrium; **MetS**, metabolic syndrome; **OR**, odds ratio; **SCD**, stearoyl CoA desaturase; **SNP**, single nucleotide polymorphism

and diacylglicerols [3]. Several studies have shown the favorable effect of a high MUFA diet on insulin sensitivity [4–7]. MUFAs are also involved in several processes as mediators of signal transduction, cellular differentiation, apoptosis, etc. [8, 9]. SCD expression is regulated by numerous factors. Glucose, fructose, or saturated FAs increase the SCD levels but PUFAs repress such expression. Because of the different functions of MUFA, variations in SCD1 activity may be involved in various processes that can lead to diseases such as obesity, diabetes, or inflammation [10].

Previous studies have shown that mice deficient in SCD are protected from obesity and insulin resistance and are characterized by having increased FA oxidation and decreased FA synthesis [11–13]. Other studies in rodents have found a high enzymatic activity in such conditions as obesity, diabetes, and insulin resistance [14, 15].

Variations in the SCD1 gene in humans might be involved in individual susceptibility to diseases such as type 2 diabetes and obesity or other related conditions. However, only a few human studies have examined the relation between variability in the SCD gene sequence and phenotypes of insulin resistance, with very disparate results [16–19]. Liew et al. [17] studied the genetic variability of the SCD1 gene in 608 diabetic persons and 600 controls, but found no differences in the genotype frequencies studied between cases and controls.. However, the study by Warensjo et al. [16], undertaken in 1143 men aged 70 years showed an association between gene polymorphisms and waist circumference, as well as insulin sensitivity. The study of Gong et al., involving 2152 subjects, evaluated the association between SCD1 gene polymorphisms and the metabolic syndrome (MetS). This study identified one tagSNP (rs1502593) (where SNP is single nucleotide polymorphisms), that was significantly associated with an increased prevalence of the MetS. Finally, Stryjecki et al. [19] examined the relationships between plasma FA, SCD1 activity, and SCD1 polymorphisms and C-reactive protein levels in young adults. They showed that one polymorphism (rs2060792) was associated with plasma levels of both individual saturated FAs and C-reactive protein.

Thus, the aim of this study was to evaluate the associations between genetic variability in the SCD1 gene, SCD1 activity, intake of oil, and obesity in a population-based prospective study (Pizarra study) in the south of Spain, for which detailed nutritional and phenotype data are available.

2 Materials and methods

2.1 Study population

The design and data collection of the Pizarra study have been described previously [20–23]. In brief, the Pizarra study is a prospective, population-based study among 1200 inhabitants of the town of Pizarra (Malaga, Spain) designed to investigate determinants of type 2 diabetes, obesity, and other related traits. The baseline study, done in 1997–1998, was completed by 1051 persons, giving a participation index of 70.3%. Participants were selected randomly from the municipal census. Six years later, in 2003–2004, the cohort was reevaluated. Those persons who had completed the baseline study were invited by letter or by phone to attend another clinical and anthropometric examination. In total, 824 persons completed the follow-up study (78.4%). Of the 227 who did not complete the study, 19 had died, 90 could not be traced, and 118 no longer wished to collaborate in the study.

All the participants were informed of the nature of the study and gave their written consent. Likewise, the participants and their family doctors were informed of the most relevant clinical results, whether or not they were abnormal. The study was approved by the Ethics and Clinical Research Committee of Carlos Haya Regional University Hospital, Malaga.

2.2 Procedures

2.2.1 Anthropometric and clinical measurements

Both at baseline and at follow-up, all the participants underwent an interview and a standardized clinical examination. In addition, several visits were made to the homes of the participants to collect nutritional data. The same methodology was used for both the baseline and the follow-up studies. Measurements were made of weight, height, and BMI. Persons were considered to be obese if their BMI was $\geq$30 kg/m^2. A fasting blood sample was drawn at baseline and at follow-up and the serum was stored at -70°C for later analysis.

2.2.2 FA composition of cooking oil and the serum phospholipids

For the baseline study, a sample was taken of the cooking oil being used by a random subset of 538 persons. To avoid the oil being swapped for newer oil, the family was unaware of the intention to request a sample of their oil until the time of the visit by the investigator. All the participants authorized the collection of their cooking oil. The FA composition of the cooking oil was analyzed by GC [20]. Cooking oil samples were classified according to their FA composition. Considering that only olive and sunflower oils are commercialized in Spain for domestic use, three groups of oils were defined: oils with levels of linoleic acid higher than 50% were classified as sunflower oils, oils with less than 25% linoleic acid were classified as olive oil, and oils containing between 25 and 50% linoleic acid were classified as mixtures. To analyze the data, the intake of oil was grouped in two categories: (i) olive oil or mixture and (ii) sunflower oil.

The FA composition of the serum phospholipids was determined by GC. SCD1 activity was estimated by using the ratio of product to precursor ([16:1/16:0] and [18:1/18:0]) [24].

2.3 SNP selection and genotyping

A total of nine SNPs were selected for genotyping based on their frequency in a Caucasian population (minor allele frequency (MAF) > 0.05), their known or possible functional effect, and their position and spacing along the SCD1 gene, as well as being the most important variants described in the literature. This information was obtained from the HapMap database (HapMap Data Rel 24-phaseII Nov08, on NCBI B36 assembly, dbSNP b126; chr10:102089500–102114800).

Genomic DNA was isolated from peripheral blood using Qiagen QIAamp DNA Blood kit in a QIACUBE instrument (QIAGEN, Crawley, UK) according to the manufacturer's recommended protocols. Genotyping was performed using the SNPlex Genotyping System based on oligo-ligation assay/PCR technology (Applied Biosystems, Foster City, California, USA). The following quality criteria were applied to the genotyped SNPs: call rate >95%, minor allele frequency > 1%, and 0.01 as *p*-value for Hardy–Weinberg equilibrium (HWE).

2.4 Statistical analysis

HWE of the nine SCD1 SNPs was tested using a χ^2 test. The continuous variables are shown as the mean and standard deviation and the classification variables as proportions. Calculation of the statistical difference between the means of the continuous variables was done by one-way analysis of variance (ANOVA) and the qualitative variables by the χ^2 test. The strength of association between variables was measured by calculating the odds ratio (OR) and 95% confidence intervals (CIs) by logistic regression. The multivariate logistic regression model was controlled for potential confounders such as age, sex, oil intake, and BMI at baseline.

To correct for multiple testing in the main analyses, we used Bonferroni to calculate the cutoff value for significance level, $0.05/9 = 0.005$. The data were analyzed with the gene analysis program R SNPassoc [25] (version 1.5.8) of the R statistical software, version 2.8.1 (Department of Statistics, University of Auckland, Auckland, New Zealand; http://www.r-project.org/).

2.4.1 Haplotype analysis

Haplotypes were estimated with those SNPs that were significantly associated with obesity. Haplotypes were implemented using Haplo.stats software (version 1.4.0) developed by the R language (http://www.r-project.org/).

3 Results

3.1 General characteristics

The baseline and follow-up characteristics of the study population are presented in Table 1. In total, 824 persons completed the follow-up study.

Table 1. General characteristics of the study population[a)]

	Baseline study ($n = 824$)	Follow-up study ($n = 824$)
Age (years)	40.6 ± 13.4	46.7 ± 13.9
Sex (male/female, %)	36.4/63.6	36.4/63.6
BMI (weight/height^2, kg/m^2)	27.6 ± 5.0	28.7 ± 5.2
Obesity (%)	29.3	36.3
Intake of olive oil (%)	75.2%	—
Plasma fatty acids levels		
Palmític (16:0)	31.7 ± 6.9	—
Palmitoleic (16:1)	0.48 ± 0.67	—
Stearic (18:0)	14.14 ± 2.2	—
Oleic (18:1)	11.53 ± 2.6	—
SCD (16:1/16:0)	0.015 ± 0.02	—
SCD(18:1/18:0)	0.83 ± 0.25	—

a) Persons who completed both the baseline and follow-up studies.
Data are means ± SD or proportions (%). Obesity: BMI ≥ 30 kg/m^2.

The genomic position and minor allele frequency of the SNPs are summarized in Supporting Information Table 1. Allele and genotype distributions of the SNPs of the SCD1 gene followed HWE proportions ($p > 0.01$).

3.2 SCD1 genetic variation and enzyme activity

At baseline, we found a significant association in four of the nine SNPs studied between the SCD1 gene and desaturase activity as measured by the 16:1/16:0 and 18:1/18:0 ratios (Table 2). Subjects who were homozygous for the minor allele had lower activity as measured by the 18:1/18:0 ratio, while homozygous subjects with the frequent allele had a lower activity index (16:1/16:0).

3.3 SCD1 genetic variation, desaturase activity, and intake of oil

We tested whether the intake of oil (olive oil versus sunflower oil) had an effect on SCD1 activity according to genotype. First, we showed that subjects who consumed preferentially olive oil had higher activity measured by 18:1/18:0 index than those who consumed sunflower oil (0.867 ± 0.23 versus 0.740 ± 0.21; $p < 0.001$). However, we did not found differences between16:1/16:0 ratio and the intake of oil. We found a significant interaction for three polymorphisms ($p = 0.009$ for rs10883463, $p = 0.02$ for rs3071, and $p = 0.04$ for rs3793767). Carriers of the minor allele of rs10883463 (CT or CC) who consumed olive oil had lower values of SCD1 activity (18:1/18:0) than those who consumed sunflower oil (0.79 ± 0.17 versus 0.94 ± 0.38). The opposite effect occurred with homozygous subjects for the T allele (Fig. 1). We found no interaction between SCD1 polymorphisms and oil intake for SCD1 activity measured by 16:1/16:0 ratio.

Table 2. Desaturation indexes of SCD1 according to genetic variation of SCD1 gene

		Desaturation index (18:1/18:0)		Desaturation index (16:1/16:0)	
		Mean ± SE	*p* value[a)]	Mean ± SE	*p* value[b)]
Rs508384	CC	0.853 ± 0.01	**0.036**	0.014 ± 0.001	**0.02**
	AC	0.838 ± 0.02		0.019 ± 0.003	
	AA	0.702 ± 0.04		0.017 ± 0.003	
Rs10883463	TT	0.852 ± 0.01	0.928	0.015 ± 0.006	**0.009**[c)]
	CT+CC	0.817 ± 0.03		0.023 ± 0.008	
RS3793768	GG	0.821 ± 0.01	0.785	0.016 ± 0.002	0.531
	GT	0.860 ± 0.01		0.015 ± 0.001	
	TT	0.852 ± 0.02		0.015 ± 0.001	
RS17669878	GG	0.857 ± 0.02	0.401	0.016 ± 0.001	0.848
	GC	0.848 ± 0.01		0.016 ± 0.001	
	CC	0.831 ± 0.02		0.014 ± 0.001	
Rs2167444	TT	0.862 ± 0.01	**0.022**	0.014 ± 0.001	**0.04**
	AT	0.841 ± 0.02		0.019 ± 0.003	
	AA	0.680 ± 0.05		0.018 ± 0.004	
Rs7849	TT	0.855 ± 0.01	**0.038**	0.014 ± 0.001	**0.02**
	CT	0.838 ± 0.02		0.019 ± 0.003	
	CC	0.702 ± 0.04		0.017 ± 0.003	
RS1502593	CC	0.852 ± 0.02	0.376	0.016 ± 0.001	0.675
	CT	0.8533 ± 0.01		0.016 ± 0.001	
	TT	0.8319 ± 0.02		0.014 ± 0.001	
RS3071	TT	0.8501 ± 0.01	0.381	0.016 ± 0.001	0.974
	TG	0.8550 ± 0.02		0.016 ± 0.001	
	GG	0.8243 ± 0.03		0.013 ± 0.001	
RS3793767	TT	0.8286 ± 0.02	0.801	0.017 ± 0.002	0.276
	TC	0.8636 ± 0.02		0.015 ± 0.001	
	CC	0.8576 ± 0.02		0.015 ± 0.001	

a) *p* value under recessive model.
b) *p* value under dominant and additive model.
c) Significant after Bonferroni correction.
Data adjusted for age and sex. Values in boldface are statistically significant.

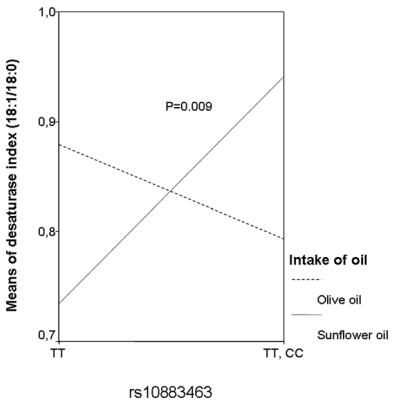

Figure 1. Interaction between intake of oil and the rs10883463 polymorphism on SCD desaturase activity. *p* value was obtained in a linear regression model adjusted for age and sex.

3.4 SNPs, obesity, and intake of olive oil

We examined whether genetic variation in the SCD1 gene could be associated with obesity. A logistic regression analysis was performed for different models: (i) baseline study and (ii) incidence study, persons who had a BMI < 30 at the baseline study and who had a BMI > 30 6 years later. In unadjusted models (adjusted only for age and sex), no SNP was associated with obesity. But when we included the intake of oil in the analysis, various polymorphisms showed a significant association with obesity (Table 3).

The SNPs rs508384 and rs7849 showed a significant association when the intake of oil was included in the analysis. Subjects with the minor allele of both polymorphisms had a lower risk of obesity. However, carriers of the minor allele of rs1502593 had a higher risk for obesity (Table 3). Among the nine SNPs studied, only rs1502593 reached statistical significance in both models. Homozygous subjects for the minor allele of rs1502593 had a greater risk of being obese 6 years later (OR = 2.5; 95% CI = 1.3–4.6). On the other hand, we tested if the obesity was also associated with the intake of oil in our population. As we expected, subjects who consumed sunflower oil had a higher risk of having obesity 6 years after than those who intake olive oil (OR = 3.018; 95% CI = 1.46–6.22; $p = 0.003$).

To evaluate the effect of the type of fat on obesity according to genotype, we performed an analysis where the participants were separated according to the type of cooking oil consumed. We observed that there was a relationship between obesity

Table 3. Association between obesity and genetic variations of SCD1 gene in a Spanish population

SNPs	Baseline study[1]				Incidence of obesity 6 years later[2]			
	OR (95% CI)[a)]	*p*	OR (95% CI)[b)]	*p*	OR (95% CI)[c)]	*p*	OR (95% CI)[d)]	*p*
RS508384 (C/A)	0.96 (0.7–1.3)	0.81	0.55 (0.3–0.9)	**0.02**	0.75 (0.4–1.3)	0.32	0.8 (0.3–1.9)	0.61
RS10883463 (T/C)	1.0 (0.5–1.7)	0.99	0.75 (0.3–1.8)	0.51	0.42 (0.1–1.3)	0.10	0.8 (0.2–3.2)	0.79
RS3793768 (G/T)	0.96 (0.7–1.2)	0.73	0.89 (0.6–1.2)	0.49	0.84 (0.5–1.2)	0.40	0.6 (0.3–1.08)	0.08
RS17669878 (G/C)	0.99 (0.8–1.2)	0.94	1.35 (0.9–1.8)	0.06	1.38 (0.9–2.0)	0.11	1.9 (1.06–3.5)	0.02
RS2167444 (T/A)	0.99 (0.7–1.4)	0.97	0.62 (0.3–1.08)	0.08	0.67 (0.3–1.2)	0.19	0.7 (0.3–1.8)	0.51
RS7849 (T/C)	0.96 (0.7–1.3)	0.82	0.54 (0.3–0.9)	**0.02**	0.7 (0.4–1.3)	0.25	0.7 (0.2–1.6)	0.39
RS1502593 (C/T)	1.1 (0.9–1.4)	0.20	1.64 (1.1–2.2)	**0.002**[e)]	1.5 (1.05–2.3)	**0.02**	2.5 (1.3–4.6)	0.002[e)]
RS3071 (T/G)	1.1 (0.9–1.4)	0.23	1.09 (0.7–1.5)	0.63	1.2 (0.8–1.8)	0.31	1.8 (1.0–3.2)	0.04
RS3793767 (T/C)	0.92 (0.7–1.1)	0.49	0.8 (0.6–1.2)	0.44	0.9 (0.6–1.3)	0.56	0.9 (0.3–1.07)	0.10

Logistic regression model. Dependent variable:
Model [1]: BMI < 30 kg/m^2 (0) versus BMI ≥ 30 kg/m^2 (1) at baseline.
Model [2]: subjects who had a BMI < 30 kg/m^2 at baseline (0) and who had a BMI ≥ 30 kg/m^2 6 years later (1).
a) Adjusted by age and sex.
b) Adjusted by age, sex, and intake of oil.
c) Adjusted by age, sex, and baseline BMI.
d) Adjusted by age, sex, baseline BMI, and intake of oil.
e) Significant after Bonferroni correction.
All *p* values under genetic additive models. Values in boldface are statistically significant.

and SCD1 polymorphisms only in the olive oil group, adjusted for age and sex (Table 4).

3.5 Haplotype and obesity

Finally, we estimated haplotypes with a frequency ≥ 0.05 (Supporting Information Table 2). The most common haplotype (frequency = 0.3738) was used as the reference (Haplo Base). Those haplotypes with a frequency lower than 0.05 were considered as rare haplotypes and were grouped in one category (hap.rare). Haplotype analysis was performed only at the baseline study because the sample size was not enough for the incidence study. An unadjusted model detected no significant associations with any of the polymorphisms. However, when intake of oil was included in the model, haplotype IV (minor alleles in rs1502593 and rs17669878) was significantly associated with obesity (OR = 1.79 (95% CI = 1.06–3.04)) (Table 5).

Table 4. Association between obesity and SCD1 polymorphisms according to intake of oil

	Olive oil		Sunflower oil	
	OR (95% CI)	*p*	OR (95% CI)	*p*
RS1502593				
CC	1.0	0.001	1.0	0.75
CT	2.4 (1.2–4.8)		0.7 (0.2–2.0)	
TT	3.6 (1.7–7.7)		1.1 (0.3–3.3)	
RS7849				
TT	1.0	0.02	1.0	0.82
CT-CC	0.49 (0.25–0.95)		1.1(0.39–3.26)	
RS508384				
CC	1.0	0.03	1.0	0.82
AC-AA	0.52 (0.27–0.99)		1.1 (0.39–3.26)	
RS17669878				
GG	1.0	0.04	1.0	0.52
CG-CC	1.8 (0.99–3.45)		0.7 (0.28–1.92)	
RS3071				
TT	1.0	0.03	1.0	0.26
GT-GG	1.7 (1.04–2.96)		0.6 (0.26–1.46)	

Logistic regression analysis: risk (OR) of obesity.
Dependent variable: no obesity, BMI < 30 kg/m^2 (0) versus obesity, BMI ≥ 30 kg/m^2 (1).
All *p* values under genetic dominant models.

4 Discussion

In this study, we evaluated the effect of SCD1 genetic variation on SCD1 activity and the presence of obesity in a population that consumes preferentially olive oil. We found that the polymorphisms rs508834, rs10883463, rs2167444, and rs7849 were associated with SCD1 desaturation indices. Furthermore, an interaction between rs10883463 and oil intake on

Table 5. Associations between common haplotypes in SCD1 gene and obesity

	Rs1502593	Rs7849	Rs508384	Rs3071	Rs17669878	Frequency	OR (95% CI)	*p* value
Unadjusted model								
Haplo base	C	T	C	T	G	0.322	1.00 (Reference haplotype)	
Hap I	C	C	A	T	G	0.122	1.07 (0.72–1.58)	0.74
Hap II	T	T	C	G	C	0.279	1.13 (0.85–1.51)	0.40
Hap III	T	T	C	T	C	0.156	1.06 (0.73–1.52)	0.76
Hap rare	*	*	*	*	*	0.120	1.06 (0.72–1.58)	0.75
Age							1.06 (1.05–1.07)	<0.001
Sex							1.47 (1.05–2.06)	0.02
Adjusted model								
Haplo base	C	T	C	T	G	0.322	1.00 (Reference haplotype)	
Hap I	C	C	A	T	G	0.113	0.61 (0.31–1.2)	0.15
Hap II	C	T	C	T	C	0.051	0.74 (0.30–1.82)	0.51
Hap III	T	T	C	G	C	0.273	1.17 (0.75–1.82)	0.48
Hap IV	T	T	C	T	C	0.154	1.79 (1.06–3.04)	0.03
Hap rare	*	*	*	*	*	0.082	1.44 (0.76–2.72)	0.25
Sunflower versus olive oil							1.47 (0.86–2.51)	0.16
Age							1.07 (1.05–1.09)	<0.001
Sex							2.06 (1.21–3.5)	0.007

Logistic regression analysis: risk (OR) of obesity.
Dependent variable: no obesity, BMI < 30 kg/m^2 (0) versus obesity, BMI ≥ 30 kg/m^2 (1) at baseline study.

the (18:1/18:0) desaturase index was found. We also showed that genetic variations in the SCD1 gene were associated with obesity; this effect was seen in both the cross-sectional study and the prospective study.

To our knowledge, only two studies have examined the relationship between SCD1 polymorphisms and enzyme activity [18, 19]. Stryjecki et al. studied the association between individual FA plasma levels and desaturation indices in both European and Asian populations. They did not identify a significant association between the different SNPs studied and SCD1 enzyme activity. However, they found a significant association between rs2060792 SNP and plasma FA in European females. Another study conducted in Costa Rican adult subjects [18] also found no association between genetic variation and enzyme activity of SCD1, although a trend where carriers of the minor allele of rs1502593 tended to have lower SCD1 indices was observed. In our study, homozygous subjects for the minor allele of rs508834, rs10883463, rs2167444, and rs7849 had lower activity measured by the 18:1/18:0 ratio, while homozygous subjects for the frequent allele showed lower values for the 16:1/16:0 index. This finding could be explained for different affinity for substrate depending on allele. This trend is shown for the four statistically associated SNPs. The presence of one or the other allele would determine the choice of substrate, which is reflected in the desaturation indices. For example, the A allele for rs508384 would have greater affinity for palmitic acid, whereas the C allele would do so for oleic acid.

Furthermore, we found a significant interaction between SCD1 polymorphisms and oil intake on (18:1/18:0) SCD1 activity. This desaturase index is influenced more by diet than the 16:1/16:0 index [26]. Subjects with the CT or CC genotypes for rs10883463 who consumed olive oil had lower values of SCD1 activity (18:1/18:0) than did those who consumed sunflower oil. The opposite effect occurred for subjects homozygous for the T allele. These results show for the first time an association between SCD1 polymorphisms, intake of oil, and desaturase activity, suggesting that genetic variation in SCD1 plays a role in regulating plasma FA levels and, consequently, in related disorders in lipid metabolism. Furthermore, this relationship cannot be independent of diet. The biological mechanism by which this interaction occurs is unknown, but it is plausible that the different affinity by substrate according to genotype together with the different type of FAs supplied by the diet can interact to exert different effects on enzymatic activity. More experimental studies are necessary to answer these questions.

In our study, as well as that of Warensjo et al., we found an association between SCD1 polymorphisms and obesity. Subjects with the rare allele of rs7849 and rs508384 had a lower risk of having obesity. By contrast, those subjects with the minor allele of rs1502593 had a higher risk of being obese. These results were adjusted for age, sex, and oil intake. In the unadjusted model, we found no significant association between polymorphisms and obesity. We showed that rs1502593 is associated with the risk of obesity not only cross-sectionally (baseline study), but also over time (this association remained significant after correction for Bonferroni). Our results are consistent with those of Gong et al., who found that rs1502593 was associated with the MetS. This SNP is located in an intronic region with no known function. We used several programs to predict possible functional effects of the SNPs studied on protein (SNP nexus, FastSNP) but no effect was predicted for this SNP. rs1502593 could be in linkage

disequilibrium with other SNPs that may account for our findings. Moreover, when we analyzed the subjects separately according to whether they consumed olive oil or sunflower oil, we observed that this association occurs only for subjects who consume olive oil. In addition, another two polymorphisms (rs17669878 and rs3071) were associated with a higher risk of having obesity in the olive oil group. The population studied is characterized by having a high intake of MUFA (mainly oleic acid). The results show that the intake of fat modifies the effect of the polymorphisms on obesity, such that those SNPs that were not significant become so after considering the type of oil, thereby implying an interaction between the two factors.

Of special interest is the consistency found in the rs7849 and rs508384 polymorphisms. The minor alleles of these SNPs were associated with a lower enzymatic activity (18:1/18:0) and in turn with a reduced risk of obesity. Warensjo et al. also found an association between both SNPs and BMI, but we showed that this association is related to lower desaturase activity. To our knowledge, no study has yet shown a significant association between genetic variation of the SCD1 gene, desaturase activity, and obesity. Our results agree with studies in animal models where SCD1 enzyme activity is high in conditions including obesity, diabetes, and insulin resistance [10, 11]. To this finding, we add that this relationship is not independent of the type of oil consumed. As expected, the effect of fat intake on desaturase activity was not found in the 16:1/16:0 SCD index. Oleic acid is a predominant FA in the diet, which may influence the product–precursor ratio as measured by oleic acid/stearic acid. The SNP rs7849 is located in the 3′UTR. This region contains functional elements involved in posttranscriptional control. Jiang et al. [27] found significant associations between three SNPs located in the 3′UTR and fat metabolism in skeletal muscle. Because of the role of these sequences in posttranscriptional regulation, polymorphisms in this region could have an effect on gene function.

These SNPs have not been associated with BMI or other obesity traits in GWAS (http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium). This fact could be explained because GWAS do not include additional information such as dietary habits (intake of oil). Our results show that the relationship between polymorphisms and obesity is not independent of the diet.

Our study adds additional information to the well-known relationship between intake of fat and obesity. Our group, among others, has shown in previous works that subjects who consumed olive oil had lower risk of being obese [28]. Increasing evidence suggests that MUFAs as a nutrient and olive oil as a food are associated with a decreased risk of cardiovascular disease, obesity, metabolic syndrome, type 2 diabetes, and hypertension [29, 30]. On the other hand, different studies have evaluated the relationship between estimated desaturase activities and dietary fat, but the results are inconclusive, probably due to differences in the study design, diet, tissue investigated, etc. [31, 32]. We have added another factor, genetic variation of SCD1 gene, to this complex process. And we show that these relationships can be modified by the genotype, as demonstrated by the found interactions.

Our study has some limitations. We estimated the enzyme activity by plasma FA ratios in phospholipids (16:1/16:0 and 18:1/18:0). Although these desaturase indices do not measure a true enzyme activity, they are widely used as biomarkers [33]. We measured the FA composition of cooking oil and of the serum phospholipids only at baseline, so we cannot evaluate the effect of polymorphisms of the SCD1 gene on desaturase activity over time. Although we tested some significant interactions, a larger sample size would be necessary to detect more interaction effects.

The strength of this study lies in its prospective nature. We evaluated the effect of genetic variation of SCD1 on several metabolic traits in a longitudinal study. Furthermore, we included in our analysis the intake of fat (type of oil). Several findings suggest that SCD1 activity is sensitive to diet, and more importantly, varies according to the genotype, so studies including this factor are necessary to elucidate the role of this desaturase on traits associated with metabolic diseases [34]. Our results show that some polymorphisms of the SCD1 gene are associated with lower activity and in turn with a reduced risk of obesity. These findings are consistent with studies in rodents relating a high enzyme activity with obesity, diabetes, and insulin resistance [11, 14].

In summary, our results show that genetic variation of the SCD1 gene may contribute to the risk of obesity, interacting with the type of dietary fat. Given the key role of SCD1 in the regulation of MUFA synthesis, our results support the hypothesis of a possible role that changes in SCD activity may have in explaining the increased prevalence of obesity in Mediterranean countries, where, unlike most other countries, the intake of MUFA accounts for around 20% of dietary calories.

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