**PPARγ Pro12Ala interacts with fat intake for obesity and weight loss in a behavioural treatment based on the Mediterranean diet**

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**Scope:** The goal of this study was to examine whether the Pro12Ala polymorphism of peroxisome proliferator-activated receptor γ (PPARγ) is associated with insulin resistance, obesity and weight loss and to analyze potential interactions between fat intake and PPARγ polymorphism in a Spanish overweight/obese population.

**Materials and methods:** We recruited 1465 subjects enrolled in a behavioural treatment program for obesity based on a Mediterranean diet, which included the following: dietary treatment, physical activity, nutritional education and behavioral techniques. A significant association was found between PPARγ Pro12Ala genotype and plasma insulin concentration and homeostasis model assessment insulin resistance. Subjects with the Ala12 genotype had lower insulin levels than those with the Pro12Pro genotype. We detected a gene–diet interaction between the PPARγ Pro12Ala polymorphism and MUFA for BMI and body fat. Furthermore, we detected an interaction between the PPARγ Pro12Ala polymorphism and fat intake for total weight loss (p < 0.001). When total fat intake was high, Ala12-carriers exhibited a significantly lower percentage of total weight loss than major-allele-carriers (p = 0.037).

**Conclusion:** Data are consistent with previous results showing a protective role for the Ala12 allele against insulin resistance, and replicate an earlier study that detected an interaction between dietary MUFA and PPARγ2 for BMI. Our detection of a gene–diet interaction between PPARγ Pro12Ala and fat intake for weight loss may explain previous discrepancies among different studies.

**Keywords:**
Fat intake / Gene–environment interaction / Obesity / Polymorphism / Peroxisome proliferator-activated receptor γ

**1 Introduction**

Peroxisome proliferator-activated receptor γ 2 gene (PPARγ2), a member of the nuclear receptor subfamily of transcription factors is involved in the expression of target genes implicated in adipocyte differentiation and glucose homeostasis [1]. A point mutation found on the B exon of the NH2-terminal of PPARγ2, substituting alanine for...
proline at position 12 (PPARγ Pro12Ala SNP) (rs1801282) has been shown to decrease receptor activity [2]. This mutation has been associated with a greater insulin sensitivity, and a more favourable lipid profile in different population studies [3–6]. These observations are consistent with previous work showing that heterozygous-deficient mice (PPARγ+/−) have increased insulin sensitivity [7]. However, in spite of this evidence, multiple studies have shown no association or an increase in the risk for Type 2 diabetes mellitus or metabolic syndrome (MetS) in people with the Ala12 variant [8, 9].

PPARγ2 is also an adipogenesis-related gene [10]. Based on this evidence, its association with obesity parameters, and more precisely, its contribution to weight loss, has been a research focus during recent years. Obesity is a complex disease, which in many cases appears as a polygenic condition affected by environmental factors. In this context, the weight loss response to dietary interventions varies widely, and predictors for successful weight reduction, including genetic factors, are poorly understood. A number of genes encoding proteins involved in the regulation of energy expenditure, energy intake, lipid metabolism and adipogenesis have been reported to alter obesity treatment outcomes [11].

Among these genes, PPARγ has been proposed as a candidate contributing to inter-individual variability in body weight reduction in response to calorie restriction. However, again conflicting results have been reported. For example, in some studies Ala carriers appear to be more responsive to lifestyle interventions that promote beneficial health effects [12], while others have reported that the PPARγ rs1801282 Pro12Ala SNP is associated with resistance to weight loss [13] or with no effect on response to weight loss intervention [14]. These discrepancies may be related to differences in intervention protocols, age of the participants, sample sizes, gene–gene interactions or gene–diet interactions.

In spite of the relatively large number of studies investigating the role of the Pro12Ala PPARγ2 variant in obesity and insulin resistance phenotypes, inconsistent results from association studies support the need for additional research. The aims of the present study were (i) to examine whether the Pro12Ala polymorphism of PPARγ is associated with insulin resistance, obesity and weight loss and (ii) to examine potential interactions between fat intake and PPARγ polymorphism in a Spanish overweight/obese population enrolled in a behavioural treatment program for obesity based on a Mediterranean diet.

2 Materials and methods

2.1 Subjects and methods

We recruited overweight or obese subjects (BMI ≥ 25 kg/m² and <40 kg/m²) within the age range of 20–65 years (n = 1465) who attended five outpatient obesity clinics during 2009–2010 in the city of Murcia, located in southeastern Spain. Patients receiving blood pressure, glucose or lipid lowering medication, or those diagnosed with diabetes mellitus, chronic renal failure, hepatic diseases or cancer were excluded from the study. All procedures were in accordance with good clinical practice. Written consent was obtained from each patient before participation and the study principles were approved by the Research Ethics Committee of the Virgen de la Arrixaca Hospital. Patient data remained confidential to guarantee anonymity.

2.2 Characteristics of the treatment

The characteristics of the weight reduction program (Garaulet method) have been described elsewhere [15, 16]. Briefly, subjects attended a weekly 60-min therapy session in support groups (n = 10) until they reached their goal weight. This period, which varied in length depending on the patient’s weight loss goal, was followed by a 5-month maintenance period. Sessions were conducted by a nutritionist. Treatment was based on the following:

Dietary treatment. Individual energy requirements were assessed by calculating (i) resting energy expenditure (REE) according to the Harris–Benedict formula and (ii) total energy expenditure (TEE) according to the type and duration of physical activity. Next, about 600 kcal/day were subtracted from the total energy expenditure. The final dietary energy content ranged from 1200 to 1800 kcal/day for women and 1500 to 2000 kcal/day for men to induce an approximate loss of 0.5–1 kg/wk. The recommendations were consistent with the Mediterranean type diet [15, 16] and the macronutrient distribution followed the recommendations of the Spanish Society of Community Nutrition [17]: 35% fat (<10% saturated and 20% monounsaturated), 50% carbohydrates and 15–20% protein. Patients were advised to consume daily unrestricted amounts of vegetables (a minimum of 200 g/day), at least 250–300 g of fruits and to use olive oil as the only cooking fat. They were also encouraged to consume the following foods for lunch: at least 100 g of legumes three times/wk, 100 g rice once/wk, 100 g wheat and pasta once/wk, and at least 1 day of fish. Recommendations for daily intake of cholesterol and fiber were <300 mg and >15 g, respectively. Patients were also rewarded with extra calories (optional calories) and extra food interchanges (floating portions) for special occasions.

Eighty-nine percent of subjects fulfilled the Mediterranean principles during the program.

Nutritional education was provided during group therapy sessions to help subjects plan their own menus and to educate subjects to adopt appropriate lifetime eating habits.

Physical activity emphasized individual goals of 15–30 min or more of moderate intensity physical activity, at least two or three times a week. Patients were encouraged to use a pedometer to reach at least 10 000 steps/day.
Behavioral techniques included stimulus control, self-monitoring, positive reinforcement and cognitive behavioural therapy. Attraction was 4–9%, depending on seasonal variation, with the highest percentage during Easter, summer and at Christmas. The main causes for dropping out were as follows: stress (37%), vacations and holidays (15%), illness or pregnancy (8%), did not want to measure food portions (6%), psychological causes (4%), incompatibility with schedule (3%), social pressures (2%) and failure to understand diet (1%). The remaining 18% reported other causes.

2.3 Habitual dietary intake

To evaluate food habits, initial nutrient intake was determined by a 24-h dietary recall. Interviews were conducted from Monday to Friday, including 24-h recalls of food intake from weekend and weekdays. Total energy intake and macronutrient composition from the initial 24-h recalls were analysed with the nutritional evaluation software program Grunumur [18] on the basis of Spanish food composition tables [19]. The intakes of fatty acids were also calculated from Spanish food composition tables [20]. The recorded intakes were typical of their usual diets. These calculations allowed us to estimate the fat percentage intakes for each type of fat based on total grams of the major saturated fatty acids (SFAs), monounsaturated fatty acids (MUFS) and polyunsaturated fatty acids (PUFS), including linoleic acid (18:2n6), linolenic acid (18:3n3) and n3 fatty acids.

2.4 DNA isolation and genotyping

DNA was isolated from blood samples using routine DNA isolation kits (Qiagen). We performed genotyping of the PPARγ2 polymorphism using a TaqMan assay with allele-specific probes on the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) according to standardized laboratory protocols [21]. We selected this specific PPARγ2 SNP based on previous research, which associated this SNP with insulin sensitivity [3–6].

2.5 Anthropometric measurements and blood pressure

Subjects were weighed barefoot wearing light clothes, with a digital scale to the nearest 0.1 kg, at the same time each day weekly to assess weight loss during treatment. Height was measured using a Harpenden digital stadiometer (rank 0.7–2.05). The subject was positioned upright, relaxed and with the head in the Frankfurt plane. BMI was calculated as weight (kg)/(height(m))². Total body fat was measured by bioelectrical impedance using TANITA TBF-300 (TANITA Corporation of America, Arlington Heights, IL, USA) equipment. Body fat distribution was assessed by the measurement of different circumferences: waist circumference, at the level of the umbilicus, and hip circumference, as the widest circumference over the greater trochanters [22]. All measurements were made with a flexible and inextensible tape measure. Blood pressure was measured seated with arm resting on a table. Blood pressure readings were recorded as millimetres of mercury (mmHg).

2.6 Biochemical analyses

Plasma glucose, cholesterol and triglycerides (TGs) and lipoprotein concentrations were determined by automated chemical analysis. VLDL-cholesterol (d < 1.006) was measured by ultracentrifugation [23]. HDL cholesterol (HDL-C) was measured after precipitation of apoB-containing lipoproteins with dextran sulphate and magnesium [24]. LDL cholesterol was calculated as total cholesterol minus HDL-C plus VLDL-cholesterol using the Friedewald equation when the TG concentration was < 4.52 mmol/L [25].

Serum insulin at baseline was measured by radioimmunoassay (Coat A Count Insulin, DCP) (assay precision:CV < 10% at 16 μIU/mL concentration, cross reactivity with proinsulin = 20%) Indices of insulin resistance: the formula for the homeostasis model assessment is as follows [26]:

\[ \text{HOMA IR} = \frac{\text{Fasting insulin} (\mu\text{IU/mL}) \times \text{Fasting glucose} (\text{mmol/L})}{22.5} \]

2.7 Statistical analyses

We used Pearson $\chi^2$ and Fisher tests to test differences in frequencies. TG, insulin and HOMA IR were log transformed. Due to the low frequency of the variant allele, carriers and non-carriers of the minor allele were grouped and compared with major allele homozygotes. We applied ANOVA and the Student t-test to compare crude means across genotype groups. We performed multivariate adjustments of the associations by analysis of covariance and estimated adjusted means. We adjusted analyses for potential confounders including sex, age and clinic. We fitted logistic regression models to estimate the odds ratio and 95% confidence interval of obesity and specific MetS components, such as high TGs, high glucose, high blood pressure and abdominal obesity associated with the PPARγ1 rs1801282 Pro12Ala SNP polymorphism. We also tested the statistical homogeneity of the effects by sex in the corresponding regression model with interaction terms. Statistical analyses were performed using SPSS 15.0 software (SPSS). A two-tailed p-value of < 0.05 was considered statistically significant.
3 Results

General characteristics of the population studied are represented in Table 1. The data characterize the subjects as overweight/obese individuals who lead sedentary lifestyles. There were no statistically significant differences associated with genotype for obesity and MetS parameters such as waist circumference, fasting plasma glucose, systolic or diastolic blood pressure, or HDL cholesterol although the weight loss rate (g/wk) was significantly lower in Ala12 carriers as compared to Pro12.

Plasma insulin concentrations and HOMA IR levels were significantly different according to PPARγ Pro12Ala genotype in that both were lower in carriers of the variant allele Ala12 than in non-carriers (p = 0.034 for insulin and p = 0.020 for HOMA IR; Table 1).

In general, the diets of these participants were unbalanced, exhibiting a lower percentage of total energy from carbohydrate than the Spanish dietary recommendations [17], along with a protein and fat intake above the recommended levels. However, participants followed the Mediterranean diet recommendations with regards to fat quality, consuming a high intake of MUFA (>50% of total fat). The distribution of the genotypes did not differ significantly from that expected according to Hardy–Weinberg equilibrium.

3.1 PPARγ Pro12Ala gene–diet interactions for obesity-related traits

When we examined whether fat intake modulated the association between PPARγ Pro12Ala variants and obesity, we evaluated the effect of total fat as a percentage of total energy and each type of fat (MUFA, SFA and PUFA) expressed as a percentage of total fat, all as categorical variables. We classified the population into high and low intake groups according to the median population intake.

We found a gene–diet interaction between the PPARγ Pro12Ala polymorphism and MUFA (% total fat) for BMI.

Table 1. General characteristics of different genotypes of the PPARγ Pro12Ala SNP

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Pro12Ala/Ala12Ala (CG/GG) n = 206</th>
<th>Pro12Pro (CC) n = 1281</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Anthropometric parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83.3</td>
<td>16.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>36.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>102.2</td>
<td>14.8</td>
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<tr>
<td>Waist:hip ratio</td>
<td>0.90</td>
<td>0.09</td>
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<tr>
<td>Weight loss (kg)</td>
<td>6.84</td>
<td>5.54</td>
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<td>Weight loss (% of initial weight)</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Weight loss rate/wk (kg)</td>
<td>0.410</td>
<td>0.360</td>
</tr>
<tr>
<td>Treatment length (n of wk)</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Physical activity (METS)</td>
<td>4439</td>
<td>8872</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<td>10</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>115</td>
<td>15</td>
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<tr>
<td>Fasting parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>52.1</td>
<td>33.3</td>
</tr>
<tr>
<td>HOMA IR (mmol/L x μU/mL/22.5)</td>
<td>1.57</td>
<td>1.18</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
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</tr>
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<td>LDL cholesterol (mmol/L)</td>
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<td>HDL-C (mmol/L)</td>
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<td>0.4</td>
</tr>
<tr>
<td>VLDL (mmol/L)</td>
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<td>0.2</td>
</tr>
<tr>
<td>TGs (mmol/L)</td>
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<td>0.5</td>
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<tr>
<td>Dietary Intake</td>
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<tr>
<td>Energy (kcal)</td>
<td>2183</td>
<td>746</td>
</tr>
<tr>
<td>Protein (% total energy)</td>
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<td>5</td>
</tr>
<tr>
<td>Carbohydrate (% total energy)</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Fat (% total energy)</td>
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<td>9</td>
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<tr>
<td>MUFA (% total fat)</td>
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<tr>
<td>PUFA (% total fat)</td>
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<td>4</td>
</tr>
<tr>
<td>SFA (% total fat)</td>
<td>29</td>
<td>8</td>
</tr>
</tbody>
</table>

a) Homozygote carriers of the major allele coding for proline (Pro12pro)(CC). Heterozygote carriers (Pro12Ala)(CG) and homozygote carriers of the alanine coding (ala12Ala)(GG). METS, metabolic equivalents.
and body fat (%) after controlling for sex, age and clinic (p for interaction = 0.039 for BMI and 0.02 for body fat; Fig. 1). Subjects carrying the Ala12 variant (minor allele G) were significantly less obese than homozygous major subjects (CC) when the MUFA intake was high (>56% of total fat) (p = 0.02), while no significant differences between carriers and non-carriers was found in the low MUFA intake group (p = 0.75) These interactions were still significant after additional adjustment for total fat intake or energy intake. No significant interactions were found between PPARγ Pro12Ala variants and total fat intake, PUFA or SFA intakes for obesity-related traits.

### 3.2 PPARγ Pro12Ala gene–diet interactions for weight loss

When we examined potential interactions between total fat intake and weight loss we found a gene–diet interaction between the PPARγ Pro12Ala polymorphism and fat intake (% of energy intake) for total weight loss (p < 0.001) (Fig. 2). Subjects carrying the PPARγ Ala12 allele (CG+G) and consuming low total fat tended to exhibit a higher percentage of total weight loss (% of initial weight) during treatment compared to Pro12 genotype (CC), although differences were not significant (p = 0.286). However, when total fat intake was high, Ala12 carriers exhibited a significantly lower percentage of total weight loss than major allele carriers (p = 0.037).

### 4 Discussion

In the current work, a significant association was found between PPARγ2 Pro12Ala genotype and plasma insulin concentration and HOMA IR, which is in agreement with earlier studies. Subjects with the Ala12 genotype had lower fasting insulin levels than those with the Pro12Pro genotype. Thamer et al. [27] hypothesized that the mechanism by which the Ala12 allele improves insulin sensitivity might involve enhanced suppression of lipidoxidation permitting more efficient glucose disposal.

First identified in 1997 by Yen et al., [31] PPARγ2 has become established as one of the most widely replicated type 2 diabetes genes. Results from European genome wide associations studies (GWAS) [28–30] have been confirmed by studies in additional ethnic groups. For example, the protective role of Ala12 allele against insulin resistance has been widely described in several populations such as Russian [4], Palestinian [32], Indian [5] and Chinese [6], and further affirmed by meta-analyses [3, 33, 34]. However, in spite of a large number of studies inconsistent and negative associations have been reported [35–37], and these may be due to differences in age [38], in genetic backgrounds, health status of the subjects, obesity degree [34] or different gene–gene [39] or gene–diet interactions [40, 41].

Consistent with numerous prior reports we did not observe direct associations between PPARγ2 Pro12Ala
genotype and BMI or other traits associated with MetS such as waist, blood pressure and plasma TG levels [42, 43]. However, we did observe a gene–diet interaction between the PPARγ2 genotype and MUFA intake for obesity. In this context obesity was attenuated in carriers of the reduced-activity Ala12 allele, but this association was significant only in subjects with high MUFA intake (≥ 56% of total fat intake). The reduced risk of obesity in Ala12 allele carriers we observed is consistent with mouse models in which lowering PPARγ2 activity, either genetically or pharmacologically, resulted in resistance to diet-induced obesity [44, 45]. In in vitro studies, the Ala12 isoform of PPARγ2 was associated with reduced transcription and reduced adipogenesis [46].

Three other groups have examined PPARγ2 Pro12Ala interaction with fatty acid intake for obesity-related traits in humans, although none of these evaluated weight loss outcomes Memisooglu et al. [40] were the first to find an interaction identical to ours in which the PPARγ2 Pro12Ala polymorphism interacted with MUFA intake for the outcome of BMI. Furthermore, an earlier study [47] detected an interaction between Pro12Ala genotype and dietary PUFA:SFA ratio, such that Ala12 allele carriers were more obese than Pro12 homozygotes when dietary PUFA:SFA ratio was low, whereas the opposite was true (i.e. Ala12 allele carriers were less obese than Pro12 homozygotes) when the PUFA:SFA ratio was high. These results were similar to ours, although in the current study Pro12Ala genotype interacted for obesity not with PUFA:SFA ratio but with MUFA%. Notably, both of these previous studies were performed in populations that habitually consumed vegetable oils that were rich in PUFA but not in oleic acid or MUFA. However, results from the current study of Mediterranean individuals who habitually consume high levels of olive oil are consistent with those from a previous report performed in another southern Spanish population [41]. In both our study and the previous cross-sectional Spanish study, MUFA consumed in the context of a Mediterranean diet was beneficial for PPARγ2 Ala12 allele carriers, although in the earlier study the outcome was insulin resistance rather than obesity.

While MUFA as supplied through a Mediterranean diet was a focus of our intervention that may be relevant to the specific interactions we detected, the overall goal of the treatment program was weight loss through reduced caloric intake. Several studies in experimental animals indicated that expression of the PPARγ2 gene was influenced by calorie restriction [48]. PPARγ2 may influence the change in body weight induced by a reduced energy intake. However, in humans, it is unclear whether PPARγ2 influences weight reduction in response to a dietary treatment. The present study is consistent with work by Adamo et al. [13] in that both studies detected resistance to weight loss in Ala12 allele carriers. The impact of high fat intake on Ala12 allele carriers could be related to altered fat metabolism. Specifically, Nicklas et al. [49] reported that women carrying the Ala12 allele experienced a reduction in resting fat oxidation after 6 months of a hypocaloric diet. However, our results conflict with those of Franks et al. [50] in which Ala12 allele carriers assigned to an intensive lifestyle intervention lost more weight and subcutaneous fat than Pro12 homozygotes. Differences could be related to the ethnic heterogeneity of the population in that study, in contrast to the current study that is limited to white subjects. Moreover, Matsuo et al. [12] after analysing six PPARγ2 SNPs, demonstrated that rs1175544 had the strongest association with weight reduction, whereas rs1801282 (Pro12Ala) was not significantly associated with weight reduction. These results could be related to their small (n = 95) population size [12].

Mechanisms underlying the role of PPARγ2 in both obesity and insulin resistance outcomes are derived from in vitro and animal models. Fatty acids, particularly unsaturated fatty acids, are ligands for PPARγ2 [51]. It has been suggested that direct PPAR activation by oleic acid may promote oxidation or sequestration of palmitate, thereby preventing deleterious effects related to SFA such as insulin resistance or cardiovascular risk [52]. Moreover, PPARγ2 activation mediates the expression of several target genes implicated in adipose tissue accumulation such as lipoprotein lipase, and also plays a role in adipose TG lipolysis [10]. Kubota et al. [53] first reported protection from dietary fat induced obesity and insulin resistance in PPARγ2-deficient (PPARγ2+/−) mice. Their results suggest that PPARγ2+/− mice are resistant to dietary-fat-induced obesity due to both decreased food intake and increased energy expenditure.

In spite of overall consistency with earlier studies supporting an important role for PPARγ2 locus in obesity, the current study also raises new questions. For example, the observed protective role of the Ala12 allele against weight gain in a high MUFA diet may appear paradoxical in light of its interference with weight loss in a high total fat diet. The physiological explanation for this phenomenon could be related to the fact that the Ala12 variant is associated with a reduced transcriptional activity and a reduced binding affinity to the cognate promoter element and reduced ability to transactivate responsive promoters [46] and consequently to a reduced activation of adipogenesis genes such as lipoprotein lipase (attenuating weight gain). However, it may also diminish the rate of weight loss based on its reduced capability for activating genes involved in adipose tissue lipolysis [54]. The overall consequence, suggested by observations in the current population, is that carriers of the Ala12 allele appear to maintain a more stable body weight than Pro12 carriers, with a greater resistance to weight gain (obesity) but also to weight loss.

The findings of the current study are notable because few human studies have investigated the role of PPARγ2 genotype, in the context of a weight loss intervention performed in a large and ethnically homogeneous population. To our knowledge, this is the first study to analyse potential
associations of $\text{PPAR}_{\gamma 2}$ and weight loss in patients following a dietary intervention based on the Mediterranean diet principles. Our detection of a gene–diet interaction may partly explain the discrepancies among different studies and populations, because diets vary widely in their fatty acid composition across different countries and even within the same country.

In summary, the current data are consistent with previous results showing a protective role for the Ala12 allele against insulin resistance, and also replicate an earlier study that detected an interaction between dietary MUFA and the $\text{PPAR}_{\gamma 2}$ locus for BMI. The particular resistance of Ala12 allele carriers to weight loss in the context of high total fat intake supports the role of $\text{PPAR}_{\gamma 2}$ in fat metabolism. Knowledge of $\text{PPAR}_{\gamma 2}$ genotype could be used predictively to guide specific dietary recommendations, which may improve weight loss outcomes in the treatment of obesity.

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The authors have declared no conflict of interest.

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