Obesity and Pro12Ala Polymorphism of Peroxisome Proliferator-Activated Receptor-Gamma Gene in Healthy Adults: A Systematic Review and Meta-Analysis

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Key Words

Obesity · Peroxisome proliferator-activated receptor-gamma · Pro12Ala polymorphism · Body mass index

Abstract

Background: The aim of this systematic review was to evaluate the relationship between obesity and peroxisome proliferator-activated receptor-gamma (PPAR γ) Pro12Ala polymorphism in healthy adults. **Summary:** Weighted mean differences (WMDs) of body mass index (BMI) were calculated for different inheritance models and subgroups. Fifty-six studies were eligible for inclusion in the meta-analysis. The result shows that the Ala allele of this polymorphism was associated with increased WMD in mean BMI (WMD = 0.29, 95% CI 0.10–0.48, $p = 0.003$). The Ala carriers were associated with increased WMD in mean BMI values in both genders and in the Caucasian subgroup. The associations were seen among people with higher levels of BMI (BMI ≥ 35). **Message:** The Ala allele of the PPAR γ Pro12Ala polymorphism in healthy adults was associated with increased BMI under a dominant model of inheritance.

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Introduction

Pathogenesis of obesity is multifactorial and involves both genetics and environmental factors [1]. Many genes are involved in regulatory pathways for weight gain and obesity. These genes include leptin, leptin receptors, melanocortin receptor 4, mitochondrial uncoupling proteins, peroxisome proliferator-activated receptor-gamma (PPAR γ), neuropeptide Y, and ghrelin as well as genes in signaling pathways [2]. PPARs are ligand-dependent transcription factors that are involved in the genetic regulation of mammalian metabolism [3]. PPAR γ plays a pivotal role in the regulation of adipocyte differentiation, energy storage, insulin sensitivity, and lipid metabolism [3]. A point mutation found on the B exon of the NH₂-terminal of PPAR γ , substitution of proline with alanine at position 12 (PPAR γ Pro12Ala SNP) (rs1801282), causes a moderate decrease in its transcription activity and adipogenic potential [4, 5]. Several meta-analyses and genome-wide association studies have confirmed the relationship between the Pro variant and the risk of type 2 diabetes [6]. Recently, new opportunities for human genome research have appeared; many studies have been conducted in this

area, but evidence for obesity is limited and inconsistent [7, 8]. Some studies have shown an association between the aforementioned single nucleotide polymorphism (SNP) and obesity [9, 10], but these have not been confirmed by other studies [11, 12]. Some systematic studies were conducted in regard to the association of this particular SNP and obesity [13–15]. However, the participants in most of the studies included were diabetic patients. Considering the fact that a significantly higher rate of overweight and obesity was found in persons with type 2 diabetes as compared to the general population, and that nutritional intervention and oral hypoglycemic agents in diabetic patients might affect their body weight [16], this study also suggested a potential interaction between this SNP and dietary intervention on body weight [17, 18]; thus, it may limit the generalizability of previous findings to healthy individuals. Therefore, the present systematic review and meta-analyses aim to investigate the association between obesity and Pro12Ala polymorphism of PPAR γ gene in healthy adults.

Methods

Search Strategy

This study was conducted with a prospective protocol, which included a predefined research question, search strategy, study eligibility criteria, and methods of data extraction and statistical analysis. We followed preferred reporting items for systematic reviews and meta-analyses guidelines for the reporting of this study [19].

We performed a systematic search for relevant studies by the 3 major databases PubMed, Embase, and Scopus in English up to April 2014, which involved humans. The key terms and medical subject heading [MeSH] were used in different combinations of the following search criteria: ‘obesity’ [MeSH], ‘obese’, ‘overweight’, ‘body weight’, ‘body fat’, ‘body mass index’, ‘BMI’, ‘skin-fold thickness’, ‘adiposity’, ‘body composition’, ‘peroxisome proliferator-activated receptor gamma’, ‘PPARgamma’ [MeSH], ‘peroxisomeproliferator-activatedreceptor-gamma2’, ‘PPARgamma2’, ‘PPARG’, ‘PPARG2’, ‘peroxisome proliferators-activated receptor’, ‘PPAR’, ‘PPAR 2’, ‘Pro12Ala’, ‘P12A’, ‘Ala12’, ‘Pro12’, ‘Ala carrier’, and ‘non-Ala carrier’. Furthermore, we reviewed reference lists of the obtained articles to search for additional studies.

Selection Criteria

The predetermined inclusion criteria of the original studies were (1) studies that included the mean BMI values for each genotype of the Pro12Ala polymorphism of PPAR γ gene (2) cohort studies, clinical trials, population case-control studies (investigating healthy participants with no matching between control and cases) or cross-sectional studies. If the data were duplicated in more than 1 study, the most recent and comprehensive study was included in the meta-analysis. Exclusion criteria included (1) studies that do not meet the inclusion criteria, (2) participants less than 18 years of age, (3) unhealthy subjects with cancer, diabetes, cardiovascular disease, polycystic ovary syndrome and other endocrine dysfunctions.

Data Extraction

All relevant articles were reviewed and duplicates deleted. Relevant articles (titles and abstracts) were screened by the authors (A.M. and M.A.) independently to select potentially articles for the review. The studies reporting our data of interest were screened for eligibility. For each included study, the following information was extracted: first author name, year of publication, mean and SD or SE of BMI by genotypes, country of study, racial background of the subjects, study design, source of the study population, gender, age, sample size, and confounding factors accounted for.

Statistical Analysis

The mean difference and SD of BMI in cohort, population case-control, cross-sectional studies, and the first data of clinical trials were considered. When SE or CI were reported, the values of SD were calculated. The frequencies of Ala/Ala homozygote in individuals are extremely rare. To ensure adequate statistical power, we included individuals with the Pro/Ala genotype along with individuals with the Ala/Ala genotype (as Ala⁺) when comparing their data with individuals with the Pro/Pro (as Ala⁻). Moreover, both dominant and recessive models were performed for studies that mentioned BMI values for Ala/Ala genotype.

Between-study heterogeneity was evaluated by Cochran’s Q statistical test and I² metric [20], which describe the percentage of total variation in point estimates attributable to genuine variation rather than sampling error, and notable considered when I² was >50% [21]. A threshold of $p < 0.1$ was used to identify the presence of heterogeneity. Random-effects models were used to calculate the pooled mean difference of BMI level in response to genotype [22]. The weighted mean difference (WMD) was used as a measure of the relationship between Pro12Ala polymorphism of PPAR γ gene and BMI. Potential sources of heterogeneity were identified in predefined subgroups including gender (male, female), ethnicity (Caucasian, Asian, and mixed populations, for example, African and Latin American), study design, and following the hypothesis that Ala carrier of this particular SNP may have a stronger effect on BMI in markedly obese persons, and in order to compare the results of the current study with those of the previous study [13], we also stratified by BMI levels (<27, 27 $\leq$, <35, and $\geq$ 35 kg/m²).

A cumulative meta-analysis was performed to show the consequence of adding studies on the effect size over time [23]. Publication bias was assessed by funnel plot and formal testing for asymmetric of funnel plot using Egger’s test [24]. The funnel plot was considered to be asymmetrical if the intercept of Egger’s regression deviation deviated from zero with $p < 0.1$. The meta-analysis was conducted using Stata software (version 12.0; StataCorp, College Station, Tex., USA). All the p values were 2-sided and the results were regarded as statistically significant if $p < 0.05$.

Results

Description of Studies

A total of 363 potentially relevant citations were retrieved by searching databases. Twelve articles were excluded because of duplication. Another 213 studies were excluded during the review because they were in vitro or review studies, studies which genotyped other PPAR γ

Fig. 1. Studies selection process.

polymorphisms, and studies with other disease or disorders population. Therefore, full text of 138 eligible articles was evaluated. After careful review of the content, another 82 studies were excluded because of missing information, reporting on the same study participants, investigating children, and including participants with a variety of disease or disorders. Finally, a total of 56 articles fulfilled the eligibility criteria and were included in the meta-analyses. The flow diagram of the selection process for the meta-analysis is displayed in figure 1.

Nine cohort studies [12, 25–32], 7 population case-control studies [33–39], 31 cross-sectional studies [5, 7, 10, 40–67], and 9 interventional studies [8, 68–75] were included in the meta-analysis of the association between PPAR γ Pro12Ala polymorphism and obesity. The characteristics and results of the studies are summarized in table 1. Seven population case-control studies [33–39], and 1 cross-sectional study [10] provided their data in 2 datasets. Each dataset was treated as a separate comparison in

the meta-analysis. Forty studies were on Caucasians [5, 8, 10, 12, 25–29, 32–39, 41–43, 45–48, 52–54, 57, 60–70], 10 studies were on Asian [31, 40, 49, 50, 55, 56, 58, 59, 71, 72] and 6 studies were on mixed populations [7, 30, 37, 73–75]. Between 56 studies, 19 studies provided data on male [10, 12, 29, 33, 35, 37, 40, 42, 43, 47, 50, 57, 60–62, 65, 66, 69, 71] and 22 studies on female members [10, 12, 29, 32, 37, 41, 42, 50, 53–55, 59–62, 64, 66, 68, 69, 72–74].

Pooled Analyses

Overall Studies

A total of 39,647 participants were included in this meta-analysis. Of these participants, 31,988 of them had Pro/Pro genotype (80.68%) and 7,623 were carriers of the Ala allele (19.22%). We performed meta-analyses on total comparisons. The pooled analysis of whole studies on the association between WMD of BMI and PPAR γ Pro12Ala polymorphism showed mild association of Ala carriers (Ala⁺) with increased WMD of BMI than

Table 1. General information of included studies

Author (reference)	Year	Country	Ethnicity	Sample size	M/F	Ala ⁻		Ala ⁺	
						n	BMI	n	BMI
<i>Cohort studies</i>									
Lindi et al. [25] [†]	2001	Finland	Caucasian	119	55/64	93	27.5±4.9	26	28.53±3.39
Schäffler et al. [26]	2001	Germany	Caucasian	359	149/210	276	27.2±6.4	83	27.47±6.31
Luan et al. [12]	2001	United Kingdom	Caucasian	592	259/333	468	26.16±5.70	124	26.19±6.05
Robitaille et al. [27]	2003	Canada	Caucasian	720	313/407	582	26.9±7.2	132	28.2±7
Pihlajamäki et al. [28]	2004	Finland	Caucasian	311	145/166	208	25.7±4.4	103	26.02±4.18
Franks et al. [29] [†]	2004	United Kingdom	Caucasian	506	226/280	399	26.56±8.47	107	26.66±7.75
Yaffe et al. [30]	2008	USA	Mixed	2,961	1,537/1,424	2,537	27.5±4.74	424	27.01±4.25
Haseeb et al. [31]	2009	India	Asian	687	425/274	538	25.71±5.74	149	25.06±5.97
Aldhoon et al. [32]	2010	Czech	Caucasian	237	F: 237	218	35.9±3.95	19	40.25±5.8
<i>Population case-control studies*</i>									
Ek et al. [33] [†]	1999	Denmark	Caucasian	Case: 752 Control: 869	M: 752 M: 869	540 641	35.5±5.5 26.2±3.7	212 228	36.29±5.85 25.9±3.17
Clement et al. [34]	2000	France	Caucasian	Case: 372 Control: 295	77/295 100/195	294 246	47±7.5 22±1.9	78 49	48±7.5 22.3±1.9
Ek et al. [35]	2001	Sweden	Caucasian	Case: 616 Control: 364	M: 616 184/180	456 270	25.6±3 23.5±3.6	160 64	25.66±3.24 23.1±3.2
Swarbrick et al. [36]	2001	Australia	Caucasian	Case: 292 Control: 371	145/147 180/191	215 277	32.9±2.6 22±1.8	77 94	32.9±2.6 22.1±2
Gonzalez et al. [37]	2002	Spain	Mixed	Case: 145 Control: 317	51/94 159/158	119 264	32.93±3.19 25.7±2.64	26 53	32.63±2.75 25.7±2.19
Ghoussaini et al. [38]	2005	France	Caucasian	Case: 507 Control: 865	NR ^c NR	397 673	40.82±8.36 23.61±3.63	110 192	40.08±7.34 24.02±3.46
Mirzaei et al. [39]	2009	Iran	Caucasian	Case: 78 Control: 78	38/40 36/42	53 65	33.30±3.40 24.60±2.90	25 13	35.10±3.30 26.60±2.20
<i>Cross-sectional studies</i>									
Deeb et al. [5] [†]	1998	Finland	Caucasian Caucasian	333 973	165/168 357/616	257 695	26.2±3.2 27.3±5.3	76 278	25±3.5 27.74±4.74
Mori et al. [40]	1998	Japan	Asian	215	M: 215	203	24.4±3.3	12	24±3
Beamer et al. [10]*	1998	USA	Caucasian Caucasian	169 517	57/112 316/201	141 408	35.3±8.31 26.1±4.04	28 109	41.5±8.46 27.3±4.18
Valve et al. [41]	1999	Finland	Caucasian	141	F: 141	107	34.5±3.8	34	35.58±3.4
Meirhaeghe et al. [42] [†]	2000	France	Caucasian	838	421/418	661	25.5±4.4	177	26.2±4.5
Poirier et al. [43]	2000	France	Caucasian	675	M: 675	507	23.3±2.25	168	23.45±3.36
Vaccaro et al. [17]	2007	Italy	Caucasian	438	315/123	365	25.6±4.4	73	26.6±4.6
Eriksson et al. [45]	2002	Finland	Caucasian	476	171/305	324	27.5±4.4	152	28±4.3
Stumvoll et al. [67]	2002	Germany	Caucasian	318	NR	242	25.8±2.48	76	24.4±4.35

Table 1. (continued)

Author (reference)	Year	Country	Ethnicity	Sample size	M/F	Ala ⁻		Ala ⁺	
						n	BMI	n	BMI
Baratta et al. [46]	2003	Italy	Caucasian	338	148/190	296	27±6	42	27±5
Rosmond et al. [47]	2003	Sweden	Caucasian	268	M: 268	186	25.9±3.4	82	26.84±4.7
Buzzetti et al. [48]	2004	Italy	Caucasian	1,215	366/849	1,008	32.8±9	207	32.4±10
Tai et al. [49]	2004	Singapore	Asian	3,080	NR	2,796	23.5±6.8	284	24.12±4.7
Takata et al. [50]	2004	Japan	Asian	247	146/101	229	21.67±2.68	18	20.5±2.06
Barbieri et al. [51]	2005	Italy	Caucasian	429	150/279	362	25±2.9	67	23.5±2.6
Meirhaeghe et al. [52] [†]	2005	France	Caucasian	1,133	NR	893	26.5±5	240	27±5.2
Tankó et al. [53]	2005	Denmark	Caucasian	1,474	F: 1,474	1,088	26.1±3.8	386	26.09±3.85
Pfab et al. [54]	2006	Germany	Caucasian	1,930	F: 1,930	1,360	22.8±4.1	570	22.83±3.95
Rhee et al. [55]	2006	Korea	Asian	253	F: 253	226	23.99±2.93	27	24.98±2.86
Canizales-Quinteros et al. [7]	2007	Mexico	Mixed	239	157/82	181	25.84±3.89	58	28.28±4.15
Hamada et al. [56]	2007	Japan	Asian	379	78/301	353	24.1±4.6	26	24.4±5.5
Helwig et al. [57]	2007	Germany	Caucasian	708	F: 708	515	27.36±4	193	27.53±4.25
Meshkani et al. [58]	2007	Iran	Asian	412	NR	340	25.73±3.9	72	25.83±4.5
Kim et al. [59] [†]	2007	Korea	Asian	129	F: 129	115	24.44±2.89	14	25.81±4.66
Mattevi et al. [60]	2007	Brazil	Caucasian	335	153/182	283	25.93±6.72	52	26.73±3.67
Morini et al. [61]	2008	Italy	Caucasian	566	211/355	501	25.28±4.34	65	26.04±4.96
Bendlová et al. [62]	2008	Czech	Caucasian	324	98/226	233	23.89±7.47	91	23.78±6.93
Ruchat et al. [63]	2009	Canada	Caucasian	680	NR	542	27.14±11.64	138	28.8±13.27
Milewicz et al. [64]	2009	Poland	Caucasian	318	F: 318	222	27.2±4.7	96	28.05±4.98
Ben Ali et al. [65]	2009	Tunis	Caucasian	387	172/215	348	39.46±5.14	39.00	40.20±5.46
Passaro et al. [66]	2011	Italy	Caucasian	364	137/227	334	30.6±5.7	30	33.2±6.3
<i>Interventional studies</i>									
Nicklas et al. [68]	2001	USA	Caucasian	70	F: 70	56	31.8±4.48	14	33.3±4.86
Thamer et al. [69]	2002	Germany	Caucasian	98	47/51	73	23.4±1.7	25	23.5±2
Lindi et al. [70] [†]	2002	Finland	Caucasian	490	161/329	337	31.1±4.4	153	31.54±4.93
Kahara et al. [71]	2003	Japan	Asian	123	M: 123	117	23.4±2.9	6	22.7±2.1
Kim et al. [72] [†]	2004	Korea	Asian	1,051	F: 1,051	977	25.46±4.06	74	26.64±4.9
Franks et al. [8] [†]	2007	USA	Caucasian	3,356	1,116/2,240	2,787	34±6.8	569	34.2±6.4
Ramírez-Salazar et al. [73]	2008	Mexico	Mixed	198	F: 198	160	29±5	38	31±5.5
Rosado et al. [74]	2010	Spain	Mixed	60	60	50	37.3±5.9	10	38.5±7.7
Garaulet et al. [75]	2011	Spain	Mixed	1,487	NR	1,281	31.2±5.4	206	30.8±5.1

* Two datasets were included; [†] the same author with different article.

M = Male; F = female; NR = not reported.

Table 2. Meta-analysis of the association between WMD of BMI and PPAR γ Pro12Ala polymorphism

Subgroups analysis	No. of studies	WMD (95% CI)	Ala ⁺ vs. Ala ⁻ p value	I ² , %	p for heterogeneity
Overall	56	0.29 (0.10 to 0.48)	0.003	60.2	<0.001
Study design					
Cohort	9	-0.08 (-0.41 to 0.23)	0.60	93.3	0.005
Population case-control	7	0.13 (-0.05 to 0.32)	0.17	39.6	0.06
Cross-sectional	31	0.20 (0.04 to 0.35)	0.01	69.2	<0.001
Interventional	9	0.23 (-0.10 to 0.56)	0.18	26.6	0.20
Sex					
Male	19	0.21 (0.01 to 0.40)	0.03	33.4	0.07
Female	22	0.26 (0.04 to 0.47)	0.01	50.2	0.003
BMI, kg/m ²					
<27	36	0.11 (-0.01 to 0.23)	0.08	63.9	<0.001
27 $\leq$ BMI <35	21	0.17 (-0.02 to 0.37)	0.09	42.2	0.02
$\geq$ 35	7	0.96 (0.32 to 1.60)	0.003	69.7	0.003
Ethnicity					
Asian	10	0.21 (0.14 to 0.56)	0.24	50.8	0.03
Mixed	6	-0.10 (-0.41 to 0.20)	0.50	76.6	<0.001
Caucasian	40	0.18 (0.06 to 0.30)	0.002	58.7	<0.001
BMI <27	24	0.06 (-0.07 to 0.21)	0.33	63.9	<0.001
27 $\leq$ BMI <35	17	0.43 (0.18 to 0.68)	0.001	0.0	0.48
BMI $\geq$ 35	6	0.96 (0.31 to 1.60)	0.003	74.7	0.001

non-Ala carriers (Ala⁻) (WMD = 0.29, 95% CI 0.10–0.48, Ala⁺ vs. Ala⁻ p = 0.003), and with significant heterogeneity (p for heterogeneity <0.001, I² = 60.2%; table 2; fig. 2). Further analyses were performed for gender, ethnicity, BMI status, and study design subgroups to investigate the source of heterogeneity (table 2). In subgroup analyses for study design, significant heterogeneity was found for cohort and cross-sectional studies (p for heterogeneity = 0.005 and <0.001, respectively), but not for interventional and population case-control studies (table 2).

Gender

Following stratification based on gender, the pooled analysis showed the association of Ala⁺ and mild increase of WMD of BMI in both male (WMD = 0.21, 95% CI 0.01–0.40, Ala⁺ vs. Ala⁻ p = 0.03) and female (WMD = 0.26, 95% CI 0.04–0.47, Ala⁺ vs. Ala⁻ p = 0.01) patients (fig. 3). Moreover, each subgroup was heterogeneous for male (p for heterogeneity = 0.07, I² = 33.4%) and for female (p for heterogeneity = 0.003, I² = 50.2%) participants.

BMI

The pooled analysis by BMI status showed a strong association between Ala⁺ and the increment of WMD of BMI for BMI $\geq$ 35 (WMD = 0.96, 95% CI 0.32–1.60, Ala⁺ vs. Ala⁻ p = 0.003), p for heterogeneity = 0.003, I² = 69.7% (table 2; fig. 4).

Ethnicity

Stratified analyses by ethnicity (Caucasian, Asian, and mixed populations) showed that the Ala⁺ was associated with increased WMD in mean BMI values in the Caucasian subgroup in comparison with Ala⁻ (WMD = 0.18, 95% CI 0.06–0.30, Ala⁺ vs. Ala⁻ p = 0.002; fig. 5). All ethnicity subgroups were heterogeneous (heterogeneity test for Caucasian p < 0.001, I² = 58.7%, for Asian p = 0.03, I² = 50.8% and for mixed populations p < 0.001, I² = 76.6%). More investigation by BMI categories in Caucasians showed that in both 27 $\leq$ BMI <35 and BMI $\geq$ 35 subgroups, Ala⁺ was associated with an increased WMD of BMI (table 2).

Pooled Analyses of Studies in Dominant and Recessive Models

Fourteen studies presented BMI values for Ala/Ala genotype. In the 14 studies under a dominant model (Pro/Pro in compared with Pro/Ala and Ala/Ala combinations), the mean BMI was higher in Ala carriers than in non-Ala carriers (WMD = 0.22, 95% CI 0.04–0.41, Pro/Ala + Ala/Ala vs. Pro/Pro p = 0.01). However, under a recessive model (Pro/Pro and Pro/Ala combined in compared with Ala/Ala), there was no significant difference between genotypes (WMD = 0.91, 95% CI -0.11 to 1.93, Ala/Ala vs. Pro/Pro + Pro/Ala p = 0.08; fig. 6).

Fig. 2. Association between PPAR γ polymorphisms and WMD of BMI. Forest plot showing individual and pooled WMD (95% CI) for the association between the PPAR γ Pro12Ala polymorphisms and BMI. * Two data-sets were included; [†] the same author with different article.

Fig. 3. Association between PPAR γ polymorphisms and WMD of BMI, in sex subgroups. Forest plot showing individual and pooled WMD (95% CI) for the association between the PPAR γ Pro12Ala polymorphisms and mean BMI by gender. Diamonds show the

WMD estimated for each subgroup. Test of overall effect: $z = 2.09$, $p = 0.03$ for male and $z = 2.38$, $p = 0.01$ for female. ⁺ Two datasets were included; [†] the same author with a different article.

Fig. 4. Association between PPAR γ polymorphisms and WMD of BMI. Forest plot showing individual and pooled WMD (95% CI) for the association between the PPAR γ Pro12Ala and BMI.

Fig. 5. Association between PPAR γ polymorphisms and WMD of BMI by ethnicity. Forest plot showing individual and pooled WMD (95% CI) for the association between the PPAR γ Pro12Ala polymorphisms and BMI by ethnicity (Caucasian, Asian and mixed population). Diamonds show the WMD estimated for each

subgroup. Test of overall effect: $z = 3.03$, $p = 0.002$ for Caucasian and $z = 1.16$, $p = 0.24$ for Asian. $z = 0.67$, $p = 0.50$ for mixed population. ⁺ Two datasets were included; [†] the same author with different article.

(For figures 4 and 5 see next pages.)

Fig. 6. a Forest plot showing individual and pooled fixed effect WMD (95% CI) for the association between the PPAR γ Pro12Ala polymorphisms and mean BMI under dominant inheritance model. Test of overall effect: $z = 2.40$, Pro/Ala + Ala/Ala vs. Pro/Pro $p = 0.01$. **b** Forest plot showing individual and pooled random

effect WMD (95% CI) for the association between the PPAR γ Pro12Ala polymorphisms and mean BMI under recessive inheritance model. Test of overall effect: $z = 1.74$, Ala/Ala vs. Pro/Pro + Pro/Ala $p = 0.08$.

Fig. 7. Funnel plot to assess publication bias. Circles indicate individual studies.

Publication Bias

Publication bias was examined by the visual funnel plot and the result of Egger's test. Distribution of funnel plot and the Egger's regression analysis did not show any asymmetric nature of the plot (fig. 7). Intercept = 0.15, 95% CI -0.07 to 0.38, $p = 0.19$, indicating there was no publication bias. The cumulative analyses showed the consistency of findings over time (figure not shown).

Discussion

This study suggested that the PPAR γ Pro12Ala polymorphism was associated with the BMI level. The Ala allele of this particular SNP is associated with an increase of 0.29 units in BMI, and this association was seen in both genders. Moreover, in the meta-analysis of ethnic subgroups, the Ala allele of this particular SNP was associated with an increase of 0.18 units in BMI in Caucasians. However, this significant relationship was not observed in the Asians and mixed populations. This difference may be explained by the discrepancy in the body weight distribution and the lifestyles of the ethnic groups. Luan et al. [12] reported a gene-diet interaction with regard to PPAR γ Pro12Ala polymorphism. They showed an inverse association between polyunsaturated to saturated fatty acids ratio with BMI and plasma insulin levels in Ala carriers [12], and in subsequent studies, the relationship between this polymorphism and nutrient intakes on BMI or waist circumference was verified [17, 18,

27]. Thus, it might be possible that different dietary patterns between ethnic groups could modulate the relationship between BMI and this particular SNP. In the meta-analysis of BMI subgroups, Ala allele was associated with an increase of 0.96 units for BMI ≥ 35 . Moreover, when meta-analysis was restricted to Caucasians, this association was observed in individuals with $27 \leq \text{BMI} < 35$ and BMI ≥ 35 .

In most studies, because of the low frequency of Ala/Ala genotype, BMI values were presented in the combined form of Pro/Ala and Ala/Ala. Thus, this meta-analysis was performed under a dominant model, which was a comparison between Pro/Pro genotype and combined form of Pro/Ala and Ala/Ala. Moreover, both recessive and dominant models were performed for studies that mentioned BMI values for Ala/Ala genotype. The results presented a significant relationship only in the dominant model. Therefore, the Ala allele of this particular SNP was associated with an increase in BMI under a dominant model of inheritance.

Previous studies investigated the relationship between this particular SNP and BMI, where a majority of participants were unhealthy individuals [13–15]. In a separate subgroup meta-analyses of diabetic and non-diabetic individuals, it was reported that this SNP effect on BMI was not observed in the diabetic group [14]. This confirms the necessity of excluding non-healthy individuals for exploring the real association, which was considered in these pooled analyses. Thus, in the present meta-analyses, only healthy adult participants were included. In agreement with our data, previous meta-analyses reported an association between Ala allele and BMI value, especially in the BMI ≥ 27 subgroup [13]. However, in this study, a stronger association between Ala carriers and increase in BMI value was observed (an increase of 0.06 in the previous study verses an increase of 0.29 units in the present study). The possible explanations for this discrepancy may be due to the inclusion of more studies in our meta-analyses and due to the inclusion of only healthy participants. Yao et al. [15] pooled 25 studies that showed that Ala carriers were associated with the obesity risk in comparison with the non-carriers; however, they used the odds ratio for obesity from different levels of BMI (≥ 24 , ≥ 30 and ≥ 95 th percentile).

A plausible mechanism of the effect of this particular SNP is probably mediated by an increase in insulin sensitivity. This may be secondary to more efficient suppression of free fatty acids release from fat tissue, where PPAR γ is expressed [76]. Stumvoll et al. [77] observed

that during the hyper-insulinaemic clamp, non-esterified fatty acids concentration was almost 50% lower in the Ala variant. More efficient suppression of lipolysis in this group could tilt the regulated balance between lipolysis and lipogenesis slightly toward lipogenesis and weight gain.

The results of this meta-analysis should be interpreted with the consideration of some limitations. First of all, we only included the studies published in English. Second, this meta-analysis showed significant inter-studies heterogeneities, which is a common problem in meta-analysis for genetic associations [78]. However, we performed subgroups analysis and showed that the study design is a main source of heterogeneity. In most of the subgroup analyses, heterogeneity remained, and this suggests that heterogeneity in our study could be due to other factors. Third, other SNPs and environmental factors involved in BMI value were not considered confounders because of

lack of sufficient data. The major strengths are the large sample size and the absence of publication bias. We also conducted extensive sensitivity analyses excluding studies that did not meet specific criteria for study design.

In conclusion, our results suggest that the Ala allele of the PPAR γ Pro12Ala polymorphism is associated with increased BMI under a dominant model of inheritance in both genders. In subgroup analyses, this relationship was seen only in the higher levels of BMI (BMI $\geq$ 35) and among Caucasians. Further studies considering gene–gene and gene–environment interaction are potentially recommended to elucidate these associations more clearly.

Disclosure Statement

None of the authors had any personal or financial conflicts of interest.

References

- 1 Kelishadi R: Childhood overweight, obesity, and the metabolic syndrome in developing countries. *Epidemiol Rev* 2007;29:62–76.
- 2 Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, Pérusse L, Bouchard C: The human obesity gene map: the 2005 update. *Obesity* 2006;14:529–644.
- 3 Auwerx J: PPAR γ , the ultimate thrifty gene. *Diabetologia* 1999;42:1033–1049.
- 4 Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J, Shuldiner AR: Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun* 1997;241:270–274.
- 5 Deeb SS, Fajas L, Nemoto M, Pihlajamäki J, Mykkänen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J: A Pro12Ala substitution in PPAR γ 2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 1998;20:284–287.
- 6 Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S: A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007;445:881–885.
- 7 Canizales-Quinteros S, Aguilar-Salinas CA, Ortiz-López MG, Rodríguez-Cruz M, Villarreal-Molina MT, Coral-Vázquez R, Huertas-Vázquez A, Hernández-Caballero A, López-Alarcón M, Brito-Zurita OR, et al: Association of PPAR γ 2 Pro12Ala variant with larger body mass index in Mestizo and Amerindian populations of Mexico. *Hum Biol* 2007;79:111–119.
- 8 Franks PW, Jablonski KA, Delahanty L, Hanson RL, Kahn SE, Altshuler D, Knowler WC, Florez JC: The Pro12Ala variant at the peroxisome proliferator-activated receptor gamma gene and change in obesity-related traits in the diabetes prevention program. *Diabetologia* 2007;50:2451–2460.
- 9 Cole SA, Mitchell BD, Hsueh WC, Pineda P, Beamer BA, Shuldiner AR, Comuzzie AG, Blangero J, Hixson JE: The Pro12Ala variant of peroxisome proliferator-activated receptor-gamma2 (PPAR-gamma2) is associated with measures of obesity in Mexican Americans. *Int J Obes Relat Metab Disord* 2000;24:522–524.
- 10 Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J, Shuldiner AR: Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma2 gene with obesity in two Caucasian populations. *Diabetes* 1998;47:1806–1808.
- 11 Siitonen N, Lindström J, Eriksson J, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Tuomilehto J, Laakso M, Uusitupa M: Association between a deletion/insertion polymorphism in the alpha2B-adrenergic receptor gene and insulin secretion and type 2 diabetes. The Finnish diabetes prevention study. *Diabetologia* 2004;47:1416–1424.
- 12 Luan J, Browne PO, Harding AH, Halsall DJ, O’Rahilly S, Chatterjee VK, Wareham NJ: Evidence for gene-nutrient interaction at the PPAR γ locus. *Diabetes* 2001;50:686–689.
- 13 Masud S, Ye S: Effect of the peroxisome proliferator activated receptor-gamma gene Pro12Ala variant on body mass index: a meta-analysis. *J Med Genet* 2003;40:773–780.
- 14 Galbete C, Toledo E, Martínez-González MA, Martínez JA, Guillén-Grima F, Martí A: Pro12Ala variant of the PPAR γ 2 gene increases body mass index: an updated meta-analysis encompassing 49,092 subjects. *Obesity (Silver Spring)* 2013;21:1486–1495.
- 15 Yao YS, Li J, Jin YL, Chen Y, He LP: Association between PPAR- γ 2 Pro12Ala polymorphism and obesity: a meta-analysis. *Mol Biol Rep* 2015;42:1029–1038.
- 16 Poljicanin T, Pavlič-Renar I, Metelko Z: Obesity in type 2 diabetes: prevalence, treatment trends and dilemmas. *Coll Antropol* 2011;35:829–834.
- 17 Vaccaro O, Lapice E, Monticelli A, Giacchetti M, Castaldo I, Galasso R, Pinelli M, Donnarumma G, Rivelles AA, Cocozza S, et al: Pro12Ala polymorphism of the PPAR γ 2 locus modulates the relationship between energy intake and body weight in type 2 diabetic patients. *Diabetes Care* 2007;30:1156–1161.
- 18 Memisoglu A, Hu FB, Hankinson SE, Manson JE, De Vivo I, Willett WC, Hunter DJ: Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. *Hum Mol Genet* 2003;12:2923–2929.
- 19 Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–269.
- 20 Lau J, Ioannidis JP, Schmid CH: Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997;127:820–826.

- 21 Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539–1558.
- 22 Van Houwelingen HC, Arends LR, Stijnen T: Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;21:589–624.
- 23 Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC: Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; 327:248–254.
- 24 Egger M, Davey Smith G, Schneider M, Mindes C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
- 25 Lindi V, Sivenius K, Niskanen L, Laakso M, Uusitupa M: Effect of the Pro12Ala polymorphism of the PPAR-gamma2 gene on long-term weight change in Finnish non-diabetic subjects. *Diabetologia* 2001;44:925–926.
- 26 Schäffler A, Barth N, Schmitz G, Zietz B, Palitzsch KD, Schölmerich J: Frequency and significance of Pro12Ala and Pro115Gln polymorphism in gene for peroxisome proliferation-activated receptor-gamma regarding metabolic parameters in a Caucasian cohort. *Endocrine* 2001;14:369–373.
- 27 Robitaille J, Després JP, Périusse L, Vohl MC: The PPAR-gamma P12A polymorphism modulates the relationship between dietary fat intake and components of the metabolic syndrome: results from the Québec family study. *Clin Genet* 2003;63:109–116.
- 28 Pihlajamäki J, Vanhala M, Vanhala P, Laakso M: The Pro12Ala polymorphism of the PPAR gamma 2 gene regulates weight from birth to adulthood. *Obes Res* 2004;12:187–190.
- 29 Franks PW, Luan J, Browne PO, Harding AH, O’Rahilly S, Chatterjee VK, Wareham NJ: Does peroxisome proliferation-activated receptor gamma genotype (Pro12Ala) modify the association of physical activity and dietary fat with fasting insulin level? *Metabolism* 2004;53:11–16.
- 30 Yaffe K, Kanaya AM, Lindquist K, Hsueh WC, Cummings SR, Beamer B, Newman A, Rosano C, Li R, Harris T: PPAR-gamma Pro12Ala genotype and risk of cognitive decline in elders. *Neurobiol Aging* 2008;29:78–83.
- 31 Haseeb A, Ilyas M, Chakrabarti S, Farooqui AA, Naik SR, Ghosh S, Suragani M, Ehtesham NZ: Single-nucleotide polymorphisms in peroxisome proliferation-activated receptor gamma and their association with plasma levels of resistin and the metabolic syndrome in a South Indian population. *J Biosci* 2009;34: 405–414.
- 32 Aldhoon B, Zamrazilová H, Aldhoon Hainerová I, Srámková P, Spálová J, Kunesová M, Bendlová B, Hainer V: Role of the PPARalpha Leu162Val and PPARGgamma2 Pro12Ala gene polymorphisms in weight change after 2.5-year follow-up in Czech obese women. *Folia Biol (Praha)* 2010;56:116–123.
- 33 Ek J, Urhammer SA, Sørensen TI, Andersen T, Auwerx J, Pedersen O: Homozygosity of the Pro12Ala variant of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2): divergent modulating effects on body mass index in obese and lean Caucasian men. *Diabetologia* 1999;42:892–895.
- 34 Clement K, Hercberg S, Passagne B, Galan P, Varroud-Vial M, Shuldiner AR, Beamer BA, Charpentier G, Guy-Grand B, Froguel P, et al: The Pro115Gln and Pro12Ala PPAR gamma gene mutations in obesity and type 2 diabetes. *Int J Obes Relat Metab Disord* 2000;24:391–393.
- 35 Ek J, Andersen G, Urhammer SA, Hansen L, Carstensen B, Borch-Johnsen K, Drivsholm T, Berglund L, Hansen T, Lithell H, et al: Studies of the Pro12Ala polymorphism of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2) gene in relation to insulin sensitivity among glucose tolerant caucasians. *Diabetologia* 2001;44:1170–1176.
- 36 Swarbrick MM, Chapman CM, McQuillan BM, Hung J, Thompson PL, Beilby JP: A Pro12Ala polymorphism in the human peroxisome proliferation-activated receptor-gamma 2 is associated with combined hyperlipidaemia in obesity. *Eur J Endocrinol* 2001;144: 277–282.
- 37 González Sánchez JL, Serrano Ríos M, Fernández Perez C, Laakso M, Martínez Larad MT: Effect of the Pro12Ala polymorphism of the peroxisome proliferation-activated receptor gamma-2 gene on adiposity, insulin sensitivity and lipid profile in the Spanish population. *Eur J Endocrinol* 2002;147:495–501.
- 38 Ghossaini M, Meyre D, Lobbens S, Charpentier G, Clément K, Charles MA, Tauber M, Weill J, Froguel P: Implication of the Pro12Ala polymorphism of the PPAR-gamma 2 gene in type 2 diabetes and obesity in the French population. *BMC Med Genet* 2005;6:11.
- 39 Mirzaei H, Akrami SM, Golmohammadi T, Doosti M, Heshmat R, Nakhjavani M, Amiri P: Polymorphism of Pro12Ala in the peroxisome proliferation-activated receptor gamma2 gene in Iranian diabetic and obese subjects. *Metab Syndr Relat Disord* 2009;7:453–458.
- 40 Mori Y, Kim-Motoyama H, Katakura T, Yasuda K, Kadowaki H, Beamer BA, Shuldiner AR, Akanuma Y, Yazaki Y, Kadowaki T: Effect of the Pro12Ala variant of the human peroxisome proliferation-activated receptor gamma 2 gene on adiposity, fat distribution, and insulin sensitivity in Japanese men. *Biochem Biophys Res Commun* 1998;251:195–198.
- 41 Valve R, Sivenius K, Miettinen R, Pihlajamäki J, Rissanen A, Deeb SS, Auwerx J, Uusitupa M, Laakso M: Two polymorphisms in the peroxisome proliferation-activated receptor-gamma gene are associated with severe overweight among obese women. *J Clin Endocrinol Metab* 1999;84:3708–3712.
- 42 Meirhaeghe A, Fajas L, Helbecque N, Cottel D, Auwerx J, Deeb SS, Amouyel P: Impact of the peroxisome proliferation activated receptor gamma2 Pro12Ala polymorphism on adiposity, lipids and non-insulin-dependent diabetes mellitus. *Int J Obes Relat Metab Disord* 2000;24:195–199.
- 43 Poirier O, Nicaud V, Cambien F, Tiret L: The Pro12Ala polymorphism in the peroxisome proliferation-activated receptor gamma2 gene is not associated with postprandial responses to glucose or fat tolerance tests in young healthy subjects: the European atherosclerosis research study II. *J Mol Med (Berl)* 2000; 78:346–351.
- 44 Vaccaro O, Mancini FP, Ruffa G, Sabatino L, Iovine C, Masulli M, Colantuoni V, Riccardi G: Fasting plasma free fatty acid concentrations and Pro12Ala polymorphism of the peroxisome proliferation-activated receptor (PPAR) gamma2 gene in healthy individuals. *Clin Endocrinol (Oxf)* 2002;57:481–486.
- 45 Eriksson JG, Lindi V, Uusitupa M, Forsén TJ, Laakso M, Osmond C, Barker DJ: The effects of the Pro12Ala polymorphism of the peroxisome proliferation-activated receptor-gamma2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* 2002;51:2321–2324.
- 46 Baratta R, Di Paola R, Spampinato D, Fini G, Marucci A, Coco A, Vigneri R, Frittitta L, Trischitta V: Evidence for genetic epistasis in human insulin resistance: the combined effect of PC-1 (K121Q) and PPARGgamma2 (P12A) polymorphisms. *J Mol Med (Berl)* 2003;81: 718–723.
- 47 Rosmond R, Chagnon M, Bouchard C: The Pro12Ala PPARGgamma2 gene missense mutation is associated with obesity and insulin resistance in Swedish middle-aged men. *Diabetes Metab Res Rev* 2003;19:159–163.
- 48 Buzzetti R, Petrone A, Ribaldo MC, Alemanno I, Zavarella S, Mein CA, Maiani F, Tiberti C, Baroni MG, Vecchi E, et al: The common PPAR-gamma2 Pro12Ala variant is associated with greater insulin sensitivity. *Eur J Hum Genet* 2004;12:1050–1054.
- 49 Tai ES, Corella D, Deurenberg-Yap M, Adiconis X, Chew SK, Tan CE, Ordovas JM: Differential effects of the C1431T and Pro12Ala PPARGgamma gene variants on plasma lipids and diabetes risk in an Asian population. *J Lipid Res* 2004;45:674–685.
- 50 Takata N, Awata T, Inukai K, Watanabe M, Ohkubo T, Kurihara S, Inaba M, Katayama S: Pro12Ala substitution in peroxisome proliferation-activated receptor gamma 2 is associated with low adiponectin concentrations in young Japanese men. *Metabolism* 2004;53: 1548–1551.
- 51 Barbieri M, Rizzo MR, Papa M, Acampora R, De Angelis L, Olivieri F, Marchegiani F, Franceschi C, Paolisso G: Role of interaction between variants in the PPARG and interleukin-6 genes on obesity related metabolic risk factors. *Exp Gerontol* 2005;40:599–604.
- 52 Meirhaeghe A, Tanck MW, Fajas L, Janot C, Helbecque N, Cottel D, Auwerx J, Amouyel P, Dallongeville J: Study of a new PPARGgamma2 promoter polymorphism and haplotype analysis in a French population. *Mol Genet Metab* 2005;85:140–148.

- 53 Tankó LB, Siddiq A, Lecoœur C, Larsen PJ, Christiansen C, Walley A, Froguel P: ACDC/adiponectin and PPAR-gamma gene polymorphisms: implications for features of obesity. *Obes Res* 2005;13:2113–2121.
- 54 Pfab T, Poralla C, Richter CM, Godes M, Słowinski T, Priem F, Halle H, Hocher B: Fetal and maternal peroxisome proliferator-activated receptor gamma2 Pro12Ala does not influence birth weight. *Obesity (Silver Spring)* 2006;14:1880–1885.
- 55 Rhee EJ, Oh KW, Lee WY, Kim SY, Oh ES, Baek KH, Kang MI, Kim SW: Effects of two common polymorphisms of peroxisome proliferator-activated receptor-gamma gene on metabolic syndrome. *Arch Med Res* 2006;37:86–94.
- 56 Hamada T, Kotani K, Tsuzaki K, Sano Y, Murata T, Tabata M, Sato S, Sakane N: Association of Pro12Ala polymorphism in the peroxisome proliferator-activated receptor gamma2 gene with small dense low-density lipoprotein in the general population. *Metabolism* 2007;56:1345–1349.
- 57 Helwig U, Rubin D, Kiosz J, Schreiber S, Fölsch UR, Nothnagel M, Döring F, Schrezenmeier J: The minor allele of the PPARgamma2 pro12Ala polymorphism is associated with lower postprandial TAG and insulin levels in non-obese healthy men. *Br J Nutr* 2007;97:847–854.
- 58 Meshkani R, Taghikhani M, Larijani B, Bahrami Y, Khatami S, Khoshbin E, Ghaemi A, Sadeghi S, Mirkhani F, Molapour A, et al: Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 (PPARgamma-2) gene is associated with greater insulin sensitivity and decreased risk of type 2 diabetes in an Iranian population. *Clin Chem Lab Med* 2007;45:477–482.
- 59 Kim K, Lee S, Valentine RJ: Association of pro12Ala polymorphism in the peroxisome proliferative-activated receptor gamma2 gene with obesity and hypertension in Korean women. *J Nutr Sci Vitaminol (Tokyo)* 2007;53:239–246.
- 60 Mattevi VS, Zembrzusi VM, Hutz MH: Effects of a PPARG gene variant on obesity characteristics in Brazil. *Braz J Med Biol Res* 2007;40:927–932.
- 61 Morini E, Tassi V, Capponi D, Ludovico O, Dallapiccola B, Trischitta V, Prudente S: Interaction between PPARgamma2 variants and gender on the modulation of body weight. *Obesity (Silver Spring)* 2008;16:1467–1470.
- 62 Bendlová B, Vejrazková D, Vcelák J, Lukášová P, Burkonová D, Kunesová M, Vrbíková J, Dvoráková K, Vondra K, Vanková M: PPAR-gamma2 Pro12Ala polymorphism in relation to free fatty acids concentration and composition in lean healthy Czech individuals with and without family history of diabetes type 2. *Physiol Res* 2008;57(suppl 1):S77–S90.
- 63 Ruchat SM, Weisnagel SJ, Vohl MC, Rankinen T, Bouchard C, Pérusse L: Evidence for interaction between PPARG Pro12Ala and PPARGC1A Gly482Ser polymorphisms in determining type 2 diabetes intermediate phenotypes in overweight subjects. *Exp Clin Endocrinol Diabetes* 2009;117:455–459.
- 64 Milewicz A, Tworowska-Bardzińska U, Dunajska K, Jędrzejuk D, Lwow F: Relationship of PPARgamma2 polymorphism with obesity and metabolic syndrome in postmenopausal Polish women. *Exp Clin Endocrinol Diabetes* 2009;117:628–632.
- 65 Ben Ali S, Ben Yahia F, Sediri Y, Kallel A, Ftouhi B, Feki M, Elasmı M, Haj-Taieb S, Souheil O, Sanhagi H, et al: Gender-specific effect of Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma-2 gene on obesity risk and leptin levels in a Tunisian population. *Clin Biochem* 2009;42:1642–1647.
- 66 Passaro A, Dalla Nora E, Marcello C, Di Vece F, Morieri ML, Sanz JM, Bosi C, Fellin R, Zuliani G: PPARγ Pro12Ala and ACE ID polymorphisms are associated with BMI and fat distribution, but not metabolic syndrome. *Cardiovasc Diabetol* 2011;10:112.
- 67 Stumvoll M, Stefan N, Fritsche A, Madaus A, Tschrutter O, Koch M, Machicao F, Häring H: Interaction effect between common polymorphisms in PPARgamma2 (Pro12Ala) and insulin receptor substrate 1 (Gly972Arg) on insulin sensitivity. *J Mol Med (Berl)* 2002;80:33–38.
- 68 Nicklas BJ, van Rossum EF, Berman DM, Ryan AS, Dennis KE, Shuldiner AR: Genetic variation in the peroxisome proliferator-activated receptor-gamma2 gene (Pro12Ala) affects metabolic responses to weight loss and subsequent weight regain. *Diabetes* 2001;50:2172–2176.
- 69 Thamer C, Haap M, Volk A, Maerker E, Becker R, Bachmann O, Machicao F, Häring HU, Stumvoll M: Evidence for greater oxidative substrate flexibility in male carriers of the Pro12Ala polymorphism in PPARgamma2. *Horm Metab Res* 2002;34:132–136.
- 70 Lindi VI, Uusitupa MI, Lindström J, Louheranta A, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, et al: Association of the Pro12Ala polymorphism in the PPAR-gamma2 gene with 3-year incidence of type 2 diabetes and body weight change in the Finnish diabetes prevention study. *Diabetes* 2002;51:2581–2586.
- 71 Kahara T, Takamura T, Hayakawa T, Nagai Y, Yamaguchi H, Katsuki T, Katsuki K, Katsuki M, Kobayashi K: PPARgamma gene polymorphism is associated with exercise-mediated changes of insulin resistance in healthy men. *Metabolism* 2003;52:209–212.
- 72 Kim KS, Choi SM, Shin SU, Yang HS, Yoon Y: Effects of peroxisome proliferator-activated receptor-gamma2 Pro12Ala polymorphism on body fat distribution in female Korean subjects. *Metabolism* 2004;53:1538–1543.
- 73 Ramirez-Salazar M, Pérez-Luque E, Fajardo-Araujo M, Garza SM, Malacara JM: Effect of the Pro12Ala polymorphism of the PPAR gamma 2 gene on response to pioglitazone treatment in menopausal women. *Menopause* 2008;15:1151–1156.
- 74 Rosado EL, Bressan J, Martínez JA, Marques-Lopes I: Interactions of the PPARγ2 polymorphism with fat intake affecting energy metabolism and nutritional outcomes in obese women. *Ann Nutr Metab* 2010;57:242–250.
- 75 Garaulet M, Smith CE, Hernández-González T, Lee YC, Ordovás JM: PPARγ Pro12Ala interacts with fat intake for obesity and weight loss in a behavioural treatment based on the Mediterranean diet. *Mol Nutr Food Res* 2011;55:1771–1779.
- 76 Stumvoll M, Wahl HG, Löblein K, Becker R, Machicao F, Jacob S, Häring H: Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-gamma2 gene is associated with increased antilipolytic insulin sensitivity. *Diabetes* 2001;50:876–881.
- 77 Stumvoll M, Häring H: Reduced lipolysis as possible cause for greater weight gain in subjects with the Pro12Ala polymorphism in PPARgamma2? *Diabetologia* 2002;45:152–153.
- 78 Munafò MR, Flint J: Meta-analysis of genetic association studies. *Trends Genet* 2004;20:439–444.