Effect of the *Pro12Ala* polymorphism of the *PPAR-γ2* gene on long-term weight change in Finnish non-diabetic subjects

To the Editor: Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a nuclear receptor that regulates adipocyte differentiation, fat-specific gene expression and insulin action [1]. Alternative use of promoters and differential splicing of the *PPAR-γ* gene result in three mRNA isoforms: *PPAR-γ1*, *PPAR-γ2* and *PPAR-γ3*. Of the three *PPAR-γ* isoforms, *PPAR-γ2* mRNA is most abundantly and relatively specifically expressed in the adipose tissue [1], which makes the *PPAR-γ2* a candidate gene for the regulation of body weight.

A missense mutation that results in a substitution of proline for alanine in codon 12 has been found in the *PPAR-γ2* gene specific exon B [2]. The association of the *Pro12Ala* polymorphism with body weight has been controversial. In cross-sectional studies the *Ala12* allele has been associated with lower [3] and higher BMI [4, 5]. However, only one previous study has examined the effect of the *Pro12Ala* polymorphism on longterm (> 5 years) body weight [6]. Therefore, we investigated the association between the *Pro12Ala* polymorphism and the longterm body weight change in Finnish non-diabetic subjects in a 10-year follow-up study.

Details of study population recruitment, the methods for the OGTT and the measurements of fasting blood glucose and plasma insulin as well as anthropometric measurements have been described [7]. The original study cohort consisted of 144 middle-aged non-diabetic subjects randomly selected from the population register of the county of Kuopio in eastern Finland [7]. The screening for the *Pro12Ala* polymorphism was done in 119 subjects (55 men and 64 women) by the PCR-SSCP method [5]. The relative weight change during the 10-year follow-up was calculated as follows: $[(\text{weight}_{\text{10-year follow-up}} - \text{weight}_{\text{baseline}})/\text{weight}_{\text{baseline}}] * 100$. The study was approved by the Ethics Committee of the University of Kuopio and the Kuopio University Hospital. Informed consent was given by all subjects studied.

The data were analysed using StatXact-4 program version 4.0.1 (Cytel Software Corporation, Cambridge, Mass., USA) and SPSS/WIN program version 9.0 (SPSS, Chicago, Ill., USA). Differences in continuous variables among the genotypes were tested with the analysis of covariance. Age, sex, BMI and antihypertensive drug treatment were used as covariates, when appropriate. At the 10-year examination, 26 subjects had an incidental finding of marginally increased 2-h plasma glucose in OGTT with non-diabetic fasting value. In addition, two originally non-diabetic subjects had been diagnosed as having Type II (non-insulin-dependent) diabetes mellitus and they were treated with oral drugs. Therefore, glucose tolerance status at the10-year examination (normal glucose tolerance or impaired glucose tolerance/Type II diabetes) was also used as a covariate when the weight change was analysed.

The frequency of the *Ala12* allele was 0.122. This is similar as reported in previous studies among white subjects [1, 8]. At the baseline study BMI did not differ among the genotypes (Table 1). During the 10-year follow-up, subjects having the *Pro12Ala* or the *Ala12Ala* genotype gained more weight than did subjects with the *Pro12Pro* genotype ($p = 0.009$ for comparison among all three genotypes). In a secondary analysis, in which the *Pro12Ala* and the *Ala12Ala* genotypes were pooled, subjects having at least one *Ala12* allele gained more weight than did subjects with the *Pro12Pro* genotype (change in weight 5.6 ± 8.6 % vs 1.8 ± 9.1 %, respectively, $p = 0.013$ after the adjustment for age, sex, glucose tolerance status and antihypertensive drug treatment). Subjects with the *Ala12Ala* genotype had lower fasting and 2-h plasma insulin concentrations (adjusted for BMI) than did subjects with the *Pro12Pro* or the *Pro12Ala* genotype both at the baseline and the 10-year examinations (Table 1).

In our study the *Ala12* allele was associated with a tendency to gain weight over time. This agrees with the previous study, in which the *Ala12Ala* genotype was associated with a lower BMI among lean subjects (BMI < 25 kg/m^2 at draft board) but

Table 1. Characteristics of the subjects by the *Pro12Ala* polymorphism of the *PPAR-γ2* gene

	Pro12Pro	*Pro12Ala*	*Ala12Ala*	*p* value
Baseline				
Number of subjects	93	23	3	
Sex (men/women)	40/53	13/10	2/1	NS
Age (years)	54.0 ± 5.4	53.8 ± 5.7	55.0 ± 7.9	NS
Weight (kg)	73.3 ± 13.6	75.4 ± 13.9	76.2 ± 4.1	NS
Body mass index (kg/m^2)	27.1 ± 4.6	27.1 ± 3.0	26.5 ± 1.9	NS
Fasting blood glucose (mmol/l)[a]	5.5 ± 0.7	5.7 ± 0.7	6.0 ± 0.5	NS
2-h blood glucose (mmol/l)[a]	6.5 ± 2.0	6.8 ± 1.9	5.4 ± 1.4	NS
Fasting plasma insulin (pmol/l)	89.8 ± 45.4	109.0 ± 83.4	82.0 ± 33.0	0.032[b]
2-h plasma insulin (pmol/l)	365.7 ± 266.5	397.6 ± 503.2	128.0 ± 58.3	0.084[b]
10-year study				
Weight (kg)	74.4 ± 14.3	78.9 ± 14.4	84.7 ± 5.1	NS
10 year change in weight (%)	1.8 ± 9.1	4.9 ± 8.7	11.2 ± 5.4	0.009[c]
Body mass index (kg/m^2)	27.5 ± 4.9	28.4 ± 3.4	29.5 ± 3.3	NS
Fasting plasma glucose (mmol/l)	6.0 ± 1.0	6.3 ± 1.8	6.1 ± 0.6	NS
2-h plasma glucose (mmol/l)	7.0 ± 2.8	7.5 ± 4.2	5.1 ± 1.0	NS
Fasting plasma insulin (pmol/l)	70.1 ± 40.0	81.8 ± 51.2	52.6 ± 26.8	0.028 [b]
2-h plasma insulin (pmol/l)	355.5 ± 304.5	397.5 ± 466.2	134.0 ± 95.7	< 0.001[b]

Data are given as means ± SD.

[a] Converted to respective plasma values

[b] *p* value indicates the significance of the differences for comparison among all three genotypes after adjustment for age, sex, body mass index, glucose tolerance status and antihypertensive drug treatment.

[c] *p* value indicates the significance of the differences for comparison among all three genotypes after adjustment for age, sex, glucose tolerance status and antihypertensive drug treatment

with a higher BMI among obese subjects (BMI > 30 kg/m^2 at draft board) during 24 years' follow-up [6]. In our study, subjects with the *Ala12Ala* genotype had lower fasting and 2-h plasma insulin concentrations at the baseline and also at the 10-year examination despite their greater weight gain, compared to those with other genotypes, which indicates a better insulin sensitivity in subjects with the *Ala12Ala* genotype. Because insulin sensitivity is suggested to be a risk factor for weight gain, a higher insulin sensitivity could explain why our subjects with the *Ala12* allele gained more weight during the follow-up than did subjects with the *Pro12Pro* genotype. It is not known, however, why subjects with the *Ala12* allele could be more insulin sensitive.

To summarise, subjects with the *Ala* allele in codon 12 of the *PPAR-γ2* gene are prone to long-term weight gain as compared to those with the common *Pro12Pro* genotype.

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