

## CORRESPONDENCE

### No Influence of the PPAR $\gamma_2$ Pro12Ala Genotype on Serum Adiponectin Concentrations in Healthy Europeans

To the Editor:

In the November 2002 issue of *Metabolism* Yamamoto et al reported reduced serum concentrations of the adipocytokine adiponectin in healthy Japanese carriers of the Pro12Ala polymorphism in the PPAR $\gamma_2$  gene.<sup>1</sup> As the genotype groups studied were comparable with respect to age, body mass index, and measures of insulin sensitivity, the authors suggested that genetic variation in the PPAR $\gamma_2$  gene may influence adiponectin serum concentrations *in vivo*. This finding prompted us to examine the effect of the Pro12Ala polymorphism on adiponectin serum levels in healthy Caucasians of the Tübingen Family Study for type 2 diabetes (Table 1). Adiponectin levels and PPAR $\gamma_2$  genotype status were available in 648 nondiabetic subjects (409 females and 239 males). The Ala allele was more frequent in this European population (23% of the subjects studied were carriers of the Ala allele, 6 subjects were homozygous for the mutation) compared to the Japanese population. No significant difference in serum adiponectin concentrations between the genotype groups was observed ( $10.77 \pm 0.25$  [Pro/Pro] v  $11.30 \pm 0.50$   $\mu\text{g/mL}$  [X/Ala],  $P = .29$  and  $P = .23$  after adjusting for sex, waist-to-hip ratio [WHR] and % body fat). In contrast to the results of Yamamoto et al, carriers of the Ala allele in this Caucasian population, if anything, tended to have higher serum adiponectin concentrations. In conclusion, we could not demonstrate an effect of the PPAR $\gamma_2$  Pro12Ala mutation on serum adiponectin concentrations. This discrepancy with the results of the Japanese group may be explained by the differences in genetic background of the populations studied. Alternatively, environmental factors (eg, food intake, fatty acid composition of the diet) or gene-environment/gene-nutrient interaction as previously demonstrated for this variant<sup>2,3</sup> may be involved.

Table 1. Subject Characteristics

	PPAR $\gamma_2$ Pro12Ala Genotype		$P$
	Pro/Pro	X/Ala	
No. of subjects (female/male)	500 (316/184)	148 (93/55)	
Age (yr)	$36 \pm 1$	$36 \pm 1$	.89
Body mass index ( $\text{kg}/\text{m}^2$ )	$26.7 \pm 0.3$	$26.5 \pm 0.5$	.46
% body fat	$28 \pm 1$	$27 \pm 1$	.37
Waist-to-hip ratio	$0.85 \pm 0.01$	$0.86 \pm 0.01$	.63
Fasting glucose ( $\text{mmol}/\text{L}$ )	$4.99 \pm 0.03$	$5.05 \pm 0.05$	.30
Fasting Insulin ( $\text{pmol}/\text{L}$ )	$55.6 \pm 2.0$	$53.8 \pm 3.2$	.75
Adiponectin ( $\mu\text{g}/\text{mL}$ )	$10.77 \pm 0.25$	$11.30 \pm 0.50$	.21

NOTE. All data are mean  $\pm$  SEM

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## REFERENCES

1. Yamamoto Y, Hirose H, Miyashita K, et al: PPAR $\gamma_2$  gene Pro12Ala polymorphism may influence serum level of an adipocyte-derived protein, adiponectin, in the Japanese population. *Metabolism* 51:1407-1409, 2002
2. Stefan N, Fritsche A, Haring H, et al: Effect of experimental elevation of free fatty acids on insulin secretion and insulin sensitivity

in healthy carriers of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene. *Diabetes* 50:1143-1148, 2001

3. Luan J, Browne PO, Harding AH, et al: Evidence for gene-nutrient interaction at the PPARgamma locus. *Diabetes* 50:686-689, 2001

## REPLY

To the Editor:

In our study,<sup>1</sup> although body mass index (BMI), plasma glucose, serum lipids, and homeostasis model assessment by insulin resistance index (HOMA-IR) were not significantly different between subjects with and without the PPAR $\gamma_2$  gene Ala12 allele, plasma adiponectin concentrations were significantly lower in subjects with this polymorphism in the Japanese population. It is noteworthy that these phenomena were observed both in men and in women. As for the mechanism, we<sup>2</sup> and others<sup>3</sup> have found a marked increase in plasma adiponectin

level in subjects treated with synthetic PPAR $\gamma$  ligands, thiazolidinediones, and *in vitro* studies have revealed that human PPAR $\gamma_2$  with Ala12 allele had reduced transactivation activity.<sup>4</sup> Taken together, we considered that it is possible that subjects with the Ala12 allele have lower adiponectin promoter activity, resulting in a lower plasma adiponectin level.

The discrepancy to the data of Thamer et al could be due to the ethnic background. In Japanese, the frequency of the Ala12 allele (0.027) was much lower than that in the Europeans (0.119). In our study in Japanese, the difference in adiponectin level was more significant in male subjects with higher BMI.<sup>1</sup> We also speculate that it is

possible that environmental factors may interact with the PPAR $\gamma_2$  gene and/or the adiponectin gene, resulting in a greater difference in adiponectin levels.

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#### REFERENCES

1. Yamamoto Y, Hirose H, Miyashita K, et al: PPAR $\gamma_2$  gene Pro12Ala polymorphism may influence serum level of an adipocyte-derived protein, adiponectin, in the Japanese population. *Metabolism* 51:1407-1409, 2002
2. Hirose H, Kawai T, Yamamoto Y, et al: Effects of pioglitazone on metabolic parameters, body fat distribution, and serum adiponectin levels in Japanese male patients with type 2 diabetes. *Metabolism* 51:314-317, 2002
3. Maeda N, Takahashi M, Funahashi T, et al: PPAR-gamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094-2099, 2001
4. Deeb SS, Fajas L, Nemoto M, et al: A Pro12Ala substitution in PPAR $\gamma_2$  associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20:284-287, 1998