

# The Pro12Ala Polymorphism of the *PPAR* $\gamma$ 2 Gene Regulates Weight from Birth to Adulthood

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## Abstract

PIHLAJAMÄKI, JUSSI, MAUNO VANHALA, PASI VANHALA, AND MARKKU LAAKSO. The Pro12Ala polymorphism of the *PPAR* $\gamma$ 2 gene regulates weight from birth to adulthood. *Obes Res.* 2004;12:187–190.

**Objective:** The Pro12Ala polymorphism in exon B of peroxisome proliferator-activated receptor  $\gamma$  2 (*PPAR* $\gamma$ 2) gene has been related to obesity, insulin resistance, and risk of type 2 diabetes. In this study, the effect of the Pro12Ala polymorphism on long-term changes in weight and body composition was investigated.

**Research Methods and Procedures:** The Pro12Ala polymorphism was genotyped in 311 subjects who participated in our previous population-based study. In that study, weight at birth, 7 years, 20 years, and 41 years, and ponderal index at birth and BMI and waist circumference at 41 years were recorded.

**Results:** The Ala12 allele of the *PPAR* $\gamma$ 2 gene was associated with high ponderal index at birth ( $2.77 \pm 0.27$  kg/m<sup>3</sup> in subjects with the Ala12Ala genotype,  $2.79 \pm 0.29$  kg/m<sup>3</sup> in subjects with the Pro12Ala genotype, and  $2.63 \pm 0.25$  kg/m<sup>3</sup> in subjects with the Pro12Pro genotype,  $p = 0.007$ , adjusted for gender) and weight at 7 years ( $p = 0.045$ ) and tended to be associated with high birth weight ( $p = 0.094$ ). Subjects with this allele gained less weight between 7 and 20 years ( $p = 0.043$ ) and more weight between 20 and 41 years ( $p = 0.001$ ) and ended up having higher waist circumference

( $p = 0.040$ ) in adulthood than did subjects with the Pro12Pro genotype.

**Discussion:** We conclude that the Pro12Ala polymorphism of the *PPAR* $\gamma$ 2 gene regulates weight and body composition from utero to adulthood.

**Key words:** *PPAR* $\gamma$ , birth weight, weight gain, ponderal index

## Introduction

The peroxisome proliferator-activated receptor  $\gamma$  2 (*PPAR* $\gamma$ 2)<sup>1</sup> gene is expressed in adipose tissue and regulates adipocyte differentiation and gene expression in adipocytes (1). The Ala12 allele in exon B of this gene has been related to insulin sensitivity (2) and weight gain (3) in adulthood. Because birth weight is associated with the risk of type 2 diabetes (4), we hypothesized that changes in weight and body composition could be present already at birth in subjects with the Ala12 allele of the *PPAR* $\gamma$ 2 gene and, thus, explain the later risk of type 2 diabetes in subjects with this allele (5). In this retrospective population study, we investigated the effect of the Pro12Ala polymorphism on weight and ponderal index at birth and on long-term weight gain and BMI and waist circumference in adulthood.

## Research Methods and Procedures

All subjects participating in the study were Finnish. The Finnish population is relatively genetically homogenous, originating mainly from southern (European) and eastern (Asian) immigration ~2000 years ago (6). Study subjects were identified from our earlier population study investigating the association of childhood obesity with the metabolic syndrome in adulthood (7). DNA was available from 311

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<sup>1</sup> Nonstandard abbreviation: *PPAR* $\gamma$ 2, peroxisome proliferator-activated receptor  $\gamma$  2; ANCOVA, analysis of covariance.

**Table 1.** Weight at birth, 7 years, 20 years, and at the age of the clinical study (41 years) and BMI and waist circumference in the clinical study according to the Pro12Ala polymorphism of the PPAR $\gamma$ 2 gene

	Genotypes of the PPAR $\gamma$ 2 gene			<i>p</i> value
	Pro12Pro ( <i>n</i> = 208)	Pro12Ala ( <i>n</i> = 85)	Ala12Ala ( <i>n</i> = 18)	
Men/women	102/106	35/50	8/10	0.464
Age at clinical study (years)	41.5 $\pm$ 4.1	41.4 $\pm$ 4.2	40.2 $\pm$ 3.8	0.430
Weight (kg)				
Birth	3.49 $\pm$ 0.51	3.47 $\pm$ 0.56	3.77 $\pm$ 0.53	0.094
7 years	23.1 $\pm$ 3.7	22.8 $\pm$ 3.5	25.5 $\pm$ 7.8	0.045
20 years	64.2 $\pm$ 11.2	61.3 $\pm$ 11.4	63.1 $\pm$ 10.8	0.228
Clinical study	76.0 $\pm$ 15.1	76.3 $\pm$ 13.6	81.6 $\pm$ 20.0	0.141
Body composition at the clinical study				
BMI (kg/m <sup>2</sup> )	25.7 $\pm$ 4.4	25.8 $\pm$ 3.8	27.1 $\pm$ 6.0	0.449
Waist (cm)	87 $\pm$ 13	89 $\pm$ 12	93 $\pm$ 17	0.040

Mean  $\pm$  SD. ANCOVA adjusted for sex.

(145 men and 166 women) of the 439 subjects. Genotyping of the Pro12Ala polymorphism of the PPAR $\gamma$ 2 gene was done as previously described (2). In that study, no genotyping errors compared with direct sequencing using single-strand conformation polymorphism analysis were observed. The degree of adiposity was estimated using ponderal index (kilograms per meters cubed) at birth and BMI (kilograms per meters squared) in adulthood. The amount of central (visceral) adiposity in the adults was estimated using waist circumference (centimeters) at the height of the umbilicus. Changes in weight gain among the genotypes were estimated as changes in relative weight [(weight – mean weight)/mean weight]  $\times$  100 between the ages of 0 and 7, 7 and 20, and 20 and 41 years. Informed consent was obtained from all subjects after the purpose and potential risks of the study were explained. The protocol was approved by the Ethics Committee of the University of Kuopio and was in accordance with the Helsinki Declaration.

#### Statistical Analysis

All basic calculations were performed with the SPSS/PC statistical program (Version 10.0 for Windows; SPSS, Inc., Chicago, IL). The differences among subjects with different genotypes of the Pro12Ala polymorphism were tested by using the ANOVA with gender as a covariate. A value of  $p < 0.05$  was considered statistically significant. All data are presented as means  $\pm$  SD.

### Results

The genotypes of the Pro12Ala polymorphism were in Hardy-Weinberg equilibrium. The Pro12Ala polymorphism

was associated with weight at the age of 7 years ( $p = 0.045$ , adjusted for gender) and tended to be associated with birth weight ( $p = 0.094$ ). No significant difference in weight at 20 years ( $p = 0.228$ ) or at the age of the clinical study (41  $\pm$  4 years) was observed ( $p = 0.141$ , Table 1). In post hoc analysis, the difference in weight was observed only between subjects with and without the Ala12Ala genotype ( $n = 18$ ). Subjects with the Ala12Ala genotype had higher weight at birth ( $p = 0.031$ ) and at 7 years ( $p = 0.016$ ) and tended to have higher weight at the age of clinical study ( $p = 0.073$ ) than subjects with the Pro12 allele (genotypes Pro12Pro and Pro12Ala combined). No difference was observed in weight at the age of 20 years between subjects with and without the Ala12Ala genotype ( $p = 0.344$ ). No effect of the Pro12Ala polymorphism on height at any age was observed (data not shown).

Subjects with the Ala12 allele (Pro12Ala or Ala12Ala) had higher ponderal index at birth (2.63  $\pm$  0.25 in subjects with the Pro12Pro genotype, 2.79  $\pm$  0.29 in subjects with the Pro12Ala genotype, and 2.77  $\pm$  0.27 kg/m<sup>3</sup> in subjects with the Ala12Ala genotype,  $p = 0.007$ ; Figure 1) and higher waist circumference ( $p = 0.040$ ) at the age of 41 years than subjects with the Pro12Pro genotype, whereas no significant difference in BMI was observed (Table 1). Subjects with both the Pro12Ala and Ala12Ala genotypes had higher ponderal index and waist circumference than subjects with the Pro12Pro genotype ( $p < 0.05$ ).

Between birth and 7 years, no significant difference was observed among genotypes in weight gain, measured as a change of relative weight at a given age ( $p = 0.773$ , Figure

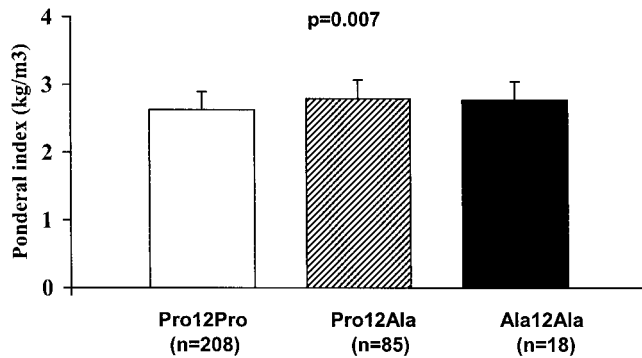


Figure 1: Ponderal index (kilograms per meters cubed) at birth according to the Pro12Ala polymorphism of the *PPAR* $\gamma$ 2 gene (ANCOVA adjusted for sex).

2). However, subjects with the *Ala12* allele gained less weight between the ages of 7 and 20 years ( $p = 0.043$ ) and more weight between the ages of 20 and 41 years ( $p = 0.001$ ) compared with subjects with the Pro12Pro genotype.

### Discussion

The association of the *Ala12* allele of the *PPAR* $\gamma$ 2 gene with high birth weight and ponderal index in this study and insulin sensitivity in earlier studies (2) is in line with the fetal insulin hypothesis suggesting that better inherited insulin action may lead to higher birth weight (8). In turn, high birth weight has been related to lower prevalence of type 2 diabetes, as observed in subjects with the *Ala12* allele (9), and cardiovascular disease (4). On the other hand, the insulin-sensitizing effect of the *Ala12* allele may explain the observed weight gain in adulthood in this and earlier studies (3). This may contribute to obesity and explain higher risk of type 2 diabetes in subjects with impaired glucose tolerance (5).

We found a difference in birth weight only between subjects with and without the *Ala12Ala* genotypes, not between subjects with the Pro12Pro and Pro12Ala genotypes. This may indicate that the *Ala12* allele has to be inherited from both parents to lead to an increased birth weight. Even though no difference in birth weight between subjects with the Pro12Pro and Pro12Ala genotypes was observed, a difference in body composition in subjects with one *Ala12* allele is likely because of higher ponderal index in subjects with this allele compared with subjects with the Pro12Pro genotype (Figure 1). The more prominent effect of the *Ala12* allele on ponderal index and waist circumference than on weight at birth or adulthood is also in line with the hypothesis that the effect of the *Ala12* allele most likely is on fat storage and not on weight in general. Finally, the possibility that another variant in this locus mediates these effects cannot be excluded, although we have not found any other significant variation in the *PPAR* $\gamma$ 2 gene among Finns (data not shown).

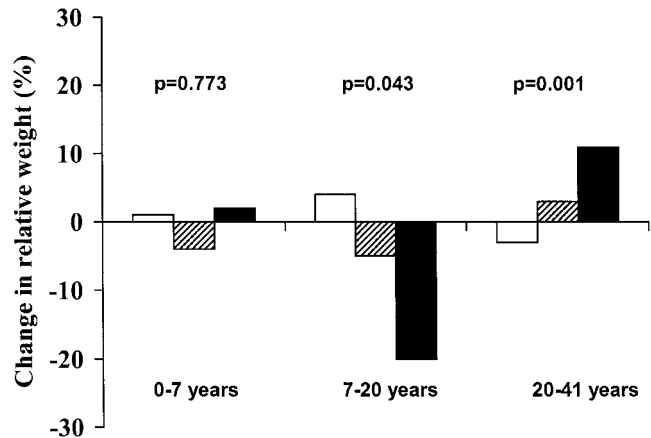


Figure 2: Change in relative weight between birth and 7 years, 7 and 20 years, and 20 and 41 years in subjects with the Pro12Pro (open bars), Pro12Ala (hatched bars), and Ala12Ala (black bars) genotypes of the *PPAR* $\gamma$ 2 gene (ANCOVA adjusted for sex).

A recent finding that an insulin-sensitizing effect of the *Ala12* allele could be observed only in subjects with low birth weight indicates that environmental factors in utero modify the action of *PPAR* $\gamma$  later in life (10). Based on our observation that birth weight and, even more significantly, ponderal index are affected by the Pro12 Ala polymorphism of the *PPAR* $\gamma$ 2 gene, we propose that *PPAR* $\gamma$ 2-environment interaction is already present in utero. Moreover, the differences in weight gain in subjects with the *Ala12* allele (i.e., low weight gain between the ages of 7 and 20 years in contrast to high weight gain in adulthood) suggest an interaction between age and the genotype. This interaction could be linked to age-related changes in lifestyle, such as changes in diet and physical activity (5,11), or it could be explained by a different action of *PPAR* $\gamma$ 2 during puberty. Finally, *PPAR* $\gamma$ 2-environment interaction may explain contradictory findings in relation to the *Ala12* allele and type 2 diabetes [i.e., low prevalence of type 2 diabetes in meta-analysis (9), but high risk in patients with impaired glucose tolerance and the metabolic syndrome (5)]. Thus, gene-lifestyle interactions are likely to regulate the effects of the Pro12Ala polymorphism on weight gain and risk of type 2 diabetes.

In summary, this study shows that the *Ala12* allele of the *PPAR* $\gamma$ 2 gene is associated with high weight and ponderal index at birth and weight gain and high waist circumference in adulthood. This action in weight regulation is likely to be modified by age-related gene-lifestyle interactions.

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