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Studies of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 (PPAR-γ2) gene in relation to insulin sensitivity among glucose tolerant Caucasians

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Abstract

Aims/hypothesis. We examined whether the Pro12-Ala polymorphism of the human peroxisome proliferator-activated receptor-γ2 (*PPAR-γ2*) gene was related to altered insulin sensitivity among glucose-tolerant subjects or a lower accumulated incidence or prevalence of IGT and Type II (non-insulin-dependent) diabetes mellitus among Scandinavian Caucasians.
Methods. The Pro12Ala polymorphism was examined using PCR-RFLP. Whole-body insulin sensitivity measured under hyperinsulinaemic-euglycaemic conditions was estimated in a population-based sample of 616 glucose tolerant Swedish Caucasian men at age 70. In addition, insulin sensitivity index was measured using IVGTT and Bergman minimal modelling in a population-based sample of 364 young healthy Danish Caucasians. Finally, we evaluated whether the polymorphism predicted Type II diabetes and IGT in 841 seventy-year-old Swedish men. A case-control study was carried out in 654 unrelated Danish Type II diabetic patients and 742 Danish glucose tolerant subjects matched for age and sex.
Results. Whole-body insulin sensitivity was significantly improved in carriers compared with non-carriers of the Ala-allele of the codon 12 polymorphism in Swedish Caucasian men (6.0 ± 2.5 vs 5.6 ± 2.5 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} $\cdot$ [mU/l]$^{-1}$ $\cdot$ 100, $p = 0.044$). The same tendency, but not significant, was observed in the insulin sensitivity index among the group of young healthy Danish Caucasians. The incidence of Type II diabetes and IGT among the Swedish subjects at the age of 70 was similar in the three genotype-groups of the Pro12Ala variant and the Ala-allele was not related to a lower prevalence of Type II diabetes in Danish Caucasians.
Conclusion/interpretation. The Ala-allele of the PPAR-γ2 polymorphism is associated with improved whole body insulin sensitivity among Swedish Caucasians. [Diabetologia (2001) 44: 1170–1176]

Keywords PPAR-γ2, polymorphism, insulin sensitivity, Type II diabetes, obesity, epidemiology, genetics.

Type II (non-insulin-dependent) diabetes mellitus is phenotypically and genetically a heterogeneous disorder resulting from defects in insulin secretion and insulin action [1]. Mutations in several genes linked to monogenic forms of Type II diabetes have been identified [2–7] and recently, a common G→A transition within intron 3 of the *CAPN10* gene (UCSNP-43) in combination with specific polymorphisms in other locations within *CAPN10* was associated with Type II diabetes [8]. However, in the vast majority of Type II diabetic patients the genetic mechanism and the pathogenesis behind the disease are still not clear.

The peroxisome proliferator-activated receptor-γ (PPAR-γ) is a transcription factor, involved in adipogenesis and in the regulation of adipocyte gene expression [9]. PPARγ exists in three different isoforms [10]. Two mutations in the ligand-binding domain of *PPAR-γ*, Pro467Leu and Val290Met, were found in

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Abbreviations: PPAR-γ, peroxisome proliferation-activated receptor-γ; OHA, oral hypoglycaemic agents

three Caucasian subjects with severe insulin resistance and Type II diabetes. Of interest, these subjects had normal body weight [11]. Within a unique domain of *PPAR-γ2* that enhances ligand-independent activation [12] a prevalent Pro12Ala polymorphism has been identified [13]. The polymorphism was shown to be involved in the pathogenesis of obesity [14–16] and a study using a family based design to control for population stratification, reported that the Ala-allele of the codon 12 polymorphism was associated with decreased risk of Type II diabetes [17]. The mechanism of these effects of the Ala-allele in PPAR-γ2 is not fully understood.

We therefore examined whether the Ala-allele of the codon 12 polymorphism of the *PPAR-γ2* gene was related to an altered insulin sensitivity of glucose tolerant subjects or whether the Ala-allele predicted a decreased risk of Type II diabetes in 70-year-old men or was associated with a lower prevalence of Type II diabetes in Scandinavian Caucasians.

Subjects and methods

Subjects. In total, 841 men from the Uppsala Health Survey Study participated in our study. Briefly, from 1970 to 1973, all 50-year-old Swedish Caucasian men ($n = 2.841$) who were born between 1920 and 1924, living in the municipality of Uppsala were invited to participate in a health survey study that originally included an intravenous glucose tolerance test (IVGTT). Those with normal fasting plasma glucose concentrations (plasma glucose < 6.7 mmol/l) and a normal intravenous glucose tolerance test (glucose disappearance rate-constant, K > 0.9) at age 50 years ($n = 1680$, baseline) [18] were invited for a re-examination in 1992 to 1994 (20-year status, at age 70 years), which included an OGTT and a hyperinsulinaemic-euglycaemic clamp [19]. The participation rate was 73 % ($n = 1.226$) and of the participants from whom DNA was available ($n = 841$), 616 were glucose tolerant and 225 had diabetes or impaired glucose tolerance (IGT) at re-examination [19]. The Ethics Committee of the Faculty of Medicine at the University of Uppsala approved the study. Further, the insulin sensitivity index was investigated in a population-based sample of 364 young healthy Danish Caucasians aged 18 to 32 years who underwent an IVGTT. The physiological characteristics of this population sample have been presented previously [20].

We did an association study on 654 unrelated Type II diabetic patients recruited from the outpatient clinic at the Steno Diabetes Center and 742 glucose tolerant control subjects matched for age and sex sampled from the same area of Copenhagen. Of the 742 control subjects, 335 were unrelated and glucose tolerant subjects sampled randomly from the Danish Central Population Register and 407 subjects were available from a population based study of 695 glucose tolerant Caucasian subjects born in 1936 who were examined in random order between May 7, 1996 and September 16, 1997, at the Copenhagen County Centre of Preventive Medicine. All investigated variables and measured standard deviations were completely comparable. The Type II diabetic patients had a mean age of clinical diabetes onset of 55 years. More than 80 % of the patients fulfilled the criteria for the metabolic syndrome according to the 1999 WHO-criteria [21], 28 % of the patients were treated with diet alone, 60 % with oral hypoglycaemic agents (OHA), and 12 % with insulin alone or in combination with OHA. Informed written consent was obtained from all subjects prior to participation and was carried out in accordance with the principles of the Helsinki Declaration II. All participants from the Danish studies were Danish Caucasians by self-identification and the ethics committee of Copenhagen approved these studies.

Measurement of clinical and biochemical variables. At age 50 years, the cohort of 841 Swedish men all underwent an IVGTT with measurements of serum insulin and plasma glucose. Subjects with treated diabetes or with fasting plasma glucose of 6.7 mmol/l or more or a disappearance rate-constant of glucose (K-value) above 0.9 during the IVGTT were excluded [18]. At age 70 whole-body insulin sensitivity was measured using a 120-min hyperinsulinaemic-euglycaemic clamp (56 mU · min^{-1} · m^{-2}) with a mean steady state of approximately 100 mU/l of serum insulin concentration [19]. Each of the 364 young healthy Danish Caucasians underwent an IVGTT after a 12-h overnight fast, i. e. an intravenous injection of 0.3 g glucose per kg body weight at time zero in combination with intravenous injection of 3 mg tolbutamide per kg body weight after 20 min [22]. The insulin sensitivity index was calculated using the Bergman MINIMOD computer programme developed specifically for the combined intravenous glucose and tolbutamide tolerance test [23]. Waist-circumference was measured midway between the lower rib and the iliac crest. Hip-circumference was measured at the point yielding the maximum circumference over the buttocks. Both variables were measured when participants were standing and to the nearest 0.5 cm. The plasma concentration of glucose in Danish subjects was measured by an automated glucose oxidase method (Granutest: Merck, Darmstadt, Germany) whereas plasma glucose in Swedish subjects was measured by a glucose dehydrogenase method. In Danish subjects the concentration of insulin (excluding des(31, 32)- and intact proinsulin) in serum was measured by ELISA using Steno Diabetes Center routine methods and in Swedish subjects it was analysed using an enzymatic-immunological assay.

Screening for the Pro12Ala polymorphism in PPAR-γ2. The screening for the Pro12Ala polymorphism was carried out on genomic DNA isolated from human leucocytes and using PCR and subsequent restriction enzyme analysis with *HpaII* [14].

Statistical methods. Significant differences in allelic frequencies between diabetic and non-diabetic subjects were examined by Fisher's exact test. Differences in continuous variables between genotypes were tested with Student's *t* test. Before analysis, the residuals were checked for normality. Values of insulin were logarithmically transformed. The tested phenotypic variables were adjusted for age, sex and BMI. Trend test and Spearman correlations analysis were used to test for gene dosage effects. We did a meta-analysis using published data on the frequency of the Pro12Ala polymorphism. In studies where genotype information was available (eight studies) we tested whether the genotype distribution was in Hardy-Weinberg equilibrium, and if the allele effect was additive. The effect of the Ala-allele was analysed on the basis of alleles, i. e. each allele gives rise to one binary observation (case or control), classified by study and allele. Analysis was done as a logistic regression with effect of size of the study and number of Ala-alleles among subjects investigated. This is equivalent to a Mantel-Haenszel analysis. It was assumed that the Ala-allele had different effects among Caucasians and Asians, and tested whether the studies among Europeans and among Asians were

Table 1. Clinical and biochemical characteristics of 616 glucose tolerant seventy-year-old Swedish Caucasian men classified according to PPAR-γ2 Pro12Ala genotype

	Pro/Pro	Pro/Ala	Ala/Ala	*p*
n	456	148	12	
BMI (kg/m^2)	25.6 ± 3.0	25.7 ± 3.1	25.2 ± 4.9	–
Waist-to-hip ratio	0.94 ± 0.05	0.94 ± 0.06	0.97 ± 0.07	–
Fasting *p*-glucose (mmol/l)	5.3 ± 0.5	5.3 ± 0.6	5.2 ± 0.2	0.14 (0.024)
Fasting *s*-insulin (mU/l)	12 ± 7	12 ± 6	11 ± 4	0.76 (0.93)
Insulin sensitivity (mg · kg^{-1} · min^{-1} · [mU/l]$^{-1}$ · 100)	5.6 ± 2.5	5.9 ± 2.5	6.5 ± 2.2	0.044 (0.041)

Data are means ± SD. Insulin sensitivity was measured from 60 to 120 min during a 2-h, hyperinsulinaemic clamp. *p* values were adjusted for BMI and compares subjects with or without the Ala-allele calculated by an unpaired Student's *t* test. *p* values (in parentheses) were obtained with trend test and Spearman correlation test after correction for BMI

Table 2. Clinical and biochemical characteristics of 364 young healthy Danish Caucasian subjects classified according to PPAR-γ2 Pro12Ala genotype

	Pro/Pro	Pro/Ala +	Ala/Ala	*p*
n (men/ women)	270 (127/143)	81 (52/29)	13 (5/8)	
Age (years)	25.2 ± 3.8	24.7 ± 3.6	26.9 ± 3.5	
BMI (kg/m^2)	23.5 ± 3.6	23.0 ± 3.0	23.8 ± 4.2	0.21
Waist-to-hip ratio	0.81 ± 0.07	0.83 ± 0.06	0.82 ± 0.06	0.19
Fasting *p*-glucose (mmol/l)	5.0 ± 0.5	5.0 ± 0.4	4.9 ± 0.4	0.23 (0.12)
Fasting *s*-insulin (pmol/l)	38 ± 22	36 ± 2 5	33 ± 16	0.71 (0.93)
Insulin sensitivity index (10^{-5} (min · pmol/l)$^{-1}$)	14.9 ± 8.6	15.8 ± 9.8	19.9 ± 16.1	0.37 (0.16)

Data are means ± SD. Insulin sensitivity index was measured applying Bergman's minimal model computing of data obtained during an intravenous glucose and tolbutamide tolerance test. *p* values were adjusted for sex, age, and BMI and compares subjects with or without the Ala-allele calculated by an unpaired Student's *t* test. *p* values (in parentheses) were obtained with trend test and Spearman correlation test after correction for sex, age, and BMI

homogeneous in relation to effect of the Ala-allele. Estimates from the logistic regression are given as odds-ratios with 95% confidence intervals. Tests were carried out as likelihood-ratio tests. All tests were two-sided and a *p* value of less than 0.05 was considered statistically significant.

Results

In the cohort of 616 normal glucose tolerant Swedish Caucasian men, a significantly higher whole-body insulin sensitivity index measured by a hyperinsulinaemic-euglycaemic clamp was found among those with at least one Ala-allele when compared to those subjects without (5.6 ± 2.5 vs 6.0 ± 2.5 mg · kg^{-1} · min^{-1} · [mU/l]$^{-1}$ · 100, $p = 0.044$) (Table 1). In the same cohort a significant trend was found towards an improved insulin sensitivity index with increasing gene dosage of the Ala-allele ($p = 0.041$) and with lowered fasting plasma glucose ($p = 0.024$) (Table 1). No differences were found in BMI or waist-to-hip ratio, between carriers and non-carriers of the Ala-allele (Table 1). In the 364 young healthy Danish Caucasians, the insulin sensitivity index using IVGTT and Bergman minimal modelling, BMI, and waist-to-hip ratio did not differ significantly between wild type, heterozygous and homozygous carriers of the Pro12Ala polymorphism in the PPAR-γ2 gene (Table 2). However, there was a non-significant tendency towards an increased insulin sensitivity index with increased gene dosage of the Ala-allele (14.9 ± 8.6 vs 15.8 ± 9.8 vs 19.9 ± 16.1 10^{-5} (min · pmol/l)$^{-1}$, trend test: $p = 0.16$, Pro12Pro vs Pro12Ala + Ala12Ala: $p = 0.37$) (Table 2).

To predict Type II diabetes and IGT, the three genotype groups of the Pro12Ala polymorphism, Pro12Pro, Pro12Ala, and Ala12Ala were investigated within the group of 841 Swedish men at the age of 70. The distribution of the three genotypes was similar in groups of Type II diabetic patients and subjects with IGT and in normal glucose tolerant subjects ($p = 0.47$) (Table 3).

The allelic frequency of the Ala-allele of the codon 12 polymorphism was 12.0% (95% CI: 9.5–14.5%) among 654 Type II diabetic patients compared to 14.0% (11.5–16.5%) among 742 glucose tolerant control subjects ($p = 0.22$) (Table 4). All genotype frequencies were in Hardy-Weinberg equilibrium.

We did a meta-analysis on all published data on the Pro12Ala variant. Analysis of eight studies with available genotype information revealed that all were in Hardy-Weinberg equilibrium and that there were additive effects of the allele. Hence, we analysed the data on the basis of alleles, also including two studies [27, 32] where the basic assumptions were not testable (Table 5). All studies showed an estimated odds ratio for the Ala-allele of 0.81 (95% CI:

Table 3. Prevalence of Type II diabetes in 841 Swedish Caucasians classified according to genotype of PPAR-γ2

Swedish subjects aged 70 after 20 years of follow-up		Distribution of genotypes among patients with Type II diabetes and IGT compared with normal glucose tolerant subjects (%)			
	Total	Pro/Pro	Pro/Ala	Ala/Ala	*p*
Subjects with Type II diabetes or IGT	225	174 (77)	49 (22)	2 (1)	
Glucose tolerant subjects	616	456 (74)	148 (24)	12 (2)	0.47

The *p* value compares the distribution of the three genotypes of PPAR-γ2 in the Type II diabetes group and the IGT group with normal glucose tolerant subjects

Table 4. PPAR-γ2 genotype frequencies among Danish Caucasian subjects

Danish Caucasians	*n*	Pro/Pro	Pro/Ala	Ala/Ala	Ala frequency (%)	95% CI	*p*
Type II diabetic patients	654	512	127	15	12.0	9.5%–14.5%	
Glucose tolerant subjects	742	552	172	18	14.0	11.5%–16.5%	0.22

The *p* value compares the allelic frequency of the codon 12 polymorphism of PPAR-γ2 in the Type II diabetes group and the allelic frequency in the control group

0.72–0.91, $p = 0.00034$). The estimated odds-ratios associated with the Ala-allele was found to be different in Caucasian (odds ratio 0.85, 95% CI: 0.76–0.96, $p = 0.0040$) and Asian populations (odds ratio: 0.42, 95% CI: 0.26–0.67, $p = 0.0067$). The difference was highly significant ($p = 0.0033$) (Table 5). We did not observe any heterogeneity within the groups of Caucasian or Asian studies ($p = 0.60$).

Discussion

Our study shows a significantly improved insulin sensitivity index measured by a hyperinsulinaemic-euglycaemic clamp associated with the Ala-allele of the Pro12Ala polymorphism in PPAR-γ2 in 616 normal glucose tolerant Swedish men. Carriers of the Ala-allele had on average a 7% increment in insulin sensitivity compared with non-carriers. Furthermore, analysis of all 841 subjects, which included Type II diabetic patients and patients with IGT revealed similar significant improvement of insulin sensitivity and also a trend for lowered fasting plasma glucose (data not shown).

Among 364 young healthy Danish Caucasians, the insulin sensitivity index applying Bergman's minimal model using IVGTT data showed a non-significant increase in insulin sensitivity index among carriers of the Ala-allele compared with non-carriers. Furthermore, a non-significantly increased insulin sensitivity was found with increased gene dosage of the Ala-allele. Thus, the same tendency towards an increased insulin sensitivity index was observed among Ala-carriers compared with non-carriers in these two study samples. However, among the young Danish subjects the increase did not reach statistical significance. We calculated the required sample size to detect a 7% increment in whole body insulin sensitivity among young Danish subjects carrying the Ala-allele. Given the standard deviation specified by Bergman's minimal model used for the sample of young Danish subjects and a power of 90%, the required sample size is about 2000 subjects. This illustrates the need for large sample sizes in genotype/phenotype interaction studies to detect small effects of a gene variant and might explain why the observed increment in insulin sensitivity index among young Danish subjects failed to reach significance. In addition, the average age of the two groups varies considerably. The Danish subjects are young and a potential influence of the variant on the insulin sensitivity index might be more pronounced later in life.

In transfection studies, the Ala-allele of the Pro12Ala polymorphism showed decreased receptor activity compared with the Pro-allele [15]. In the same study, in 333 lean non-diabetic middle-aged Finnish subjects the Pro12Ala polymorphism was associated with lower BMI ($p = 0.027$) and improved insulin sensitivity ($p = 0.047$) as determined by an IVGTT applying Bergman's minimal model [15]. However, when the insulin sensitivity index was adjusted for BMI, the differences were no longer significant [15].

The Ala-allele of the polymorphism was also shown to be associated with an increased insulin sensitivity index in a subgroup of 19 obese subjects (BMI > 30 kg/m^2) chosen from 108 offspring from Type II diabetic patients [24]. When the whole group of offspring was analysed no significant association between the polymorphism and insulin sensitivity was found [24]. In an extended group of offspring from Type II diabetic patients in the same group of investigators showed a significantly improved insulin sensitivity index among carriers compared with non-carriers of the Ala-allele in two groups comprising 37 subjects, matched for sex, BMI, fat-distribution and body composition ($p = 0.039$) [25].

Table 5. Allelic frequencies of the Ala-allele of the Pro12Ala variant of PPAR-γ2 found in ten association studies of Type II diabetic patients and glucose tolerant control subjects

Subjects	Reference		Allelic frequencies				
		n (Diabetic patients/control subjects)	Diabetic patients	Control subjects	Odds-ratio	95% CI	*p*
German Caucasians	[28]	503/310	0.14	0.15	0.97	0.72–1.29	0.89
Italian Caucasians	[27]	131/312	0.13	0.18	0.67	0.44–1.01	0.30
French Caucasians	[30]	170/839	0.10	0.11	0.87	0.59–1.28	0.51
French Caucasians	[29]	402/295	0.080	0.086	0.95	0.65–1.38	0.77
Scandinavian Caucasians	[17]	481/481	0.146	0.168	0.85	0.66–1.09	0.071
French Canadian Caucasians	[17]	127/127	0.094	0.135	0.68	0.39–1.18	0.080
Danish Caucasians	Present study	654/742	0.12	0.14	0.84	0.67–1.04	0.22
Korean subjects	[31]	58/111	0.043	0.045	0.96	0.32–2.86	1.00
Japanese-Americans	[15]	91/54	0.022	0.092	0.22	0.06–0.72	0.028
Japanese subjects	[32]	415/541	0.018	0.043	0.41	0.23–0.73	0.0030
Meta-analysis based on all published studies					0.81	0.72–0.91	0.00034
Meta-analysis based on studies of Caucasians					0.85*	0.76–0.96	0.0040
Meta-analysis based on studies of Asians					0.42*	0.26–0.67	0.0067

Fisher's exact test was applied to examine for significant differences in allele frequencies between diabetic and non-diabetic subjects. Analysis was done as a logistic regression with effect of size of the study and number of Ala-alleles among subjects investigated to examine for significant differences between diabetic and non-diabetic subjects among all published studies. Tests were carried out as likelihood-ratio tests
*($p = 0.0033$)

Decreased insulin sensitivity plays a central part in the pathogenesis of Type II diabetes [26]. In our study, the prevalence of the Ala-allele of the codon 12 polymorphism in the *PPAR-γ2* gene did not differ significantly between 654 unrelated Type II diabetic patients and 742 glucose tolerant control subjects. The findings of a similar accumulated incidence of Type II diabetes in the three groups of different genotypes of the Pro12Ala polymorphism in the prospective study of 841 Swedish men are consistent with these data. The allelic frequencies are comparable with four previous studies of Caucasian subjects and one study of Korean subjects [27–31] which showed no association of the polymorphism with Type II diabetes. In contrast, an association to a lower frequency of the Ala-allele with Type II diabetes was reported in a cohort comprising 91 Type II diabetic (allelic frequency: 2.2%) and 155 glucose tolerant (allelic frequency: 9.3%) second-generation Japanese-Americans ($p = 0.028$) [15] and among 415 Type II diabetic Japanese patients (allelic frequency: 1.8%) compared with 541 glucose tolerant control subjects (allelic frequency: 4.3%, $p < 0.05$) [32] (Table 5). However, among 215 non-diabetic Japanese men, living in Japan, the allelic frequency of the Ala-allele was 3% [33], which suggests an incidentally high frequency of the Ala-allele among the glucose tolerant control subjects in these studies [15, 33]. Recently, using a family based association study approach it was shown that the Ala-allele of the codon 12 polymorphism was associated with a decreased risk of diabetes [17]. Subsequent analysis in 1.130 individuals from Scandinavian sibships discordant for Type II diabetes, 481 case-control pairs from Scandinavia, and 127 case-control pairs from Canada showed a modest but significant ($p = 0.045$) increase in diabetes risk associated with the more common Pro-allele. A meta-analysis of all published studies, revealed an estimated risk ratio for the Ala-allele of 0.79 [17]. Of interest, our data show a similar but non-significant odds ratio of 0.84 and the updated meta-analysis shows an estimated odds ratio for the Ala-allele of 0.81. In addition, the present meta-analysis includes data from our study and a recently published association study of Korean Type II diabetic patients and normal glucose tolerant subjects [31].

Differences in the degree of obesity among the patients studied could partly explain the discrepancy of effect of the Pro12Ala polymorphism in single centre studies on diabetes risk and especially the divergent findings in Caucasian and Asian populations [15, 17, 27–32]. Asian populations tend to have lower BMI compared with Caucasians populations, probably partly because of environmental influences and lifestyle [33] but the differing prevalence of common mutations suggests that these differences could also be explained

by variation in genetic background. Furthermore, a strong interaction has been found between the dietary fat intake and the Pro12Ala polymorphism for both BMI and fasting plasma insulin [34]. This gene-nutrient interaction could explain the heterogeneity of findings in different ethnic groups. Therefore, Asian studies might contribute heavily as an important single factor for the decreased risk of diabetes associated with the Ala-allele found in the meta-analysis of all published studies. In our analysis we found a significant ($p = 0.0033$) difference between Caucasian and Asian odds ratios, but still, a significantly decreased risk for developing diabetes in a meta-analysis comprising only Caucasian subjects ($p = 0.0040$).

The study of prediction of Type II diabetes and IGT in Swedish Caucasians seems to argue against the results of the meta-analysis of the prevalence of Type II diabetes. However, this discrepancy could be apparent because of the lack of statistical power. In our association study, the difference between allelic frequencies was two percent. To detect a two percent difference in allelic frequencies between diabetic patients and control subjects we calculated the number of participants necessary in one association study to be about 5000 subjects in each group, indicating the need for large population samples and/or meta-analysis in order to detect variants with a modest effect in the pathogenesis of Type II diabetes. In aggregate, we have shown a significant association of the Ala-allele of the Pro12Ala polymorphism with increased whole body insulin sensitivity in Swedish Caucasians. Therefore, it is likely that increased insulin sensitivity is one of the mechanisms by which the Ala-allele protects against Type II diabetes.

In conclusion, we found a modestly improved insulin sensitivity associated with the Ala-allele of the PPAR-γ2 polymorphism. This might add to explain the minor protective effect of this allele against the risk of Type II diabetes seen in a meta-analysis of ten published case-control studies.

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