Genetic epistasis of adiponectin and *PPAR* γ 2 genotypes in modulation of insulin sensitivity: a family-based association study

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Abstract

Aims/hypothesis. Genetic interactions in modulating the phenotypes of a complex trait, such as insulin sensitivity, were usually taken for granted. However, this has not been commonly shown. Previous studies have suggested that both *PPAR* γ 2 and *adiponectin* genes could influence insulin sensitivity. Therefore it is likely that they could modulate insulin sensitivity through gene to gene interactions.

Methods. We genotyped 1793 subjects of Chinese and Japanese descendents from 601 hypertensive families recruited in Sapphire study for a *T94G* in the *adiponectin* gene exon 2 and the *PPAR* γ 2 *Pro12Ala* polymorphisms. Serum insulin concentrations and insulin resistance index (HOMA_{IR}) were used as the markers of insulin sensitivity.

Results. We found that the *T* allele of *adiponectin* gene was associated with a higher Ins_{60} and higher area under curve of insulin (AUC_i) in OGTT utilizing

all subjects in a mixed model that corrected for family effects. Important interactions between *adiponectin* and *PPAR* γ 2 genotypes were found in fasting insulin concentrations (Ins_0), insulin concentrations at 2-h (Ins_{120}) in OGTT and insulin resistance index (HOMA_{IR}). The main effects of the *PPAR* γ 2 genotypes were in the plasma glucose concentrations in OGTT. In contrast, the main effects of *adiponectin* genotypes were in every insulin variable, including Ins_0 , Ins_{60} , Ins_{120} , AUC_i and HOMA_{IR} . The subjects carrying the *adiponectin G* allele and the *PPAR* γ 2 *Ala12* allele seemed to be more insulin sensitive.

Conclusion/interpretation. These results showed that *adiponectin* is a genetic factor associated with insulin sensitivity. Interactions with *PPAR* γ 2 genotypes modified this association. [Diabetologia (2003) 46:977–983]

Keywords *Adiponectin*, *PPAR* γ 2, polymorphisms, gene interaction, insulin sensitivity.

Type 2 diabetes mellitus (T2DM) has daunted many countries in the developed or developing world [1]. Insensitivity to insulin stimulation is generally accepted

to be the fundamental pathophysiology of T2DM [2]. As a classical example of polygenic (also called multifactorial or complex) diseases, the pathogenesis of T2DM is attributed to the collective actions of many genetic and environmental factors and the complex interactions among them [3]. The contribution of gene to gene interactions in shaping the phenotypes of T2DM, such as insulin sensitivity, is usually taken for granted. However, it is only occasionally shown [4, 5].

Among many potential thrifty genes, the *Pro12Ala* variants of the human *PPAR* γ 2 gene have been extensively surveyed in many genetic association studies by other investigators [6, 7, 8]. Previously we reported the association of the *PPAR* γ 2 *Ala12* variant with bet-

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Abbreviations: PPAR, peroxisome proliferator-activated receptor; HOMA, homeostasis model assessment; T2DM, Type 2 diabetes mellitus.

ter glucose tolerance and insulin sensitivity among subjects from Japanese and Chinese hypertension families in the Stanford Asia Pacific Program in Hypertension and Insulin Resistance (Sapphire) study [9]. Due to its family-based study design utilizing the comparisons between siblings, the genetic association study in Sapphire was expected to have better control in early childhood environmental factors and genetic background than a population-based genetic association study [9, 10, 11].

The other sensible genetic candidates for T2DM are adipose-derived secreted molecules regulated by *PPAR* γ 2, such as leptin, resistin and adiponectin. Among them, the recombinant adiponectin protein has been shown in mice to be capable of lowering plasma glucose and fatty acids, improving insulin sensitivity and reducing body weight [12, 13, 14]. It has also been reported that *adiponectin* genotypes in humans influence insulin sensitivity and the risk for T2DM [15, 16, 17, 18, 19]. Recent studies using knockout mice confirmed these biological functions of *adiponectin* [20, 21].

We have shown that treating T2DM patients with rosiglitazone, a *PPAR* γ 2 agonist raised their plasma adiponectin concentrations by more than two-fold [22]. The other investigators have also shown that the administration of glitazones increased the expression of *adiponectin* in humans as well as in animals and in cultured adipocytes [23, 24, 25, 26]. These results together suggest a possibility of genetic interactions between *PPAR* γ 2 and *adiponectin*, and its attribution to insulin sensitivity.

In this study, we investigated the association of *adiponectin* *T94G* polymorphism with metabolic phenotypes and the effects of its interaction with the *PPAR* γ 2 *Pro12Ala* polymorphism on these phenotypes among the large cohort from the Sapphire [9, 10]. We found that the *T* allele of *adiponectin* was associated with post-glucose load hyperinsulinaemia. The main effects of the *adiponectin* and *PPAR* γ 2 genotypes and the genetic interactions between them on the metabolic variables were revealed in further analyses. The subjects having both the *G* allele of *adiponectin* and the *Ala12* allele of *PPAR* γ 2 seemed to be more insulin sensitive.

Subjects and methods

Subjects and phenotypic characterization. The characteristics of study population, the inclusion and exclusion criteria of Sapphire study were detailed in several previous publications [9, 10]. Notably, diabetic subjects diagnosed based on the WHO criteria were excluded [27]. This study incorporated both the concordant (both hypertension) and the discordant sibling-pairs (one hypertension, the other hypotension) in design. A total of 2525 subjects of Japanese or Chinese descendants were recruited from 6 centres at San Francisco, Hawaii and Taiwan. In this report, 1793 subjects including parents and

siblings from 601 families were genotyped. Written informed consent was obtained from all participants. The study was approved by the ethics board of each participating institute. Characterization of the subjects by fasting plasma glucose, insulin, triglyceride, total cholesterol, lipoprotein profile, and anthropometric measurements, including height, weight, waist and hip circumference were described in detail previously [9, 10]. A 75-g OGTT was carried out and plasma glucose and insulin concentration at 1-h and 2-h post-glucose load were measured [9, 10]. The fasting plasma sample was obtained right before the OGTT was conducted.

Extraction of genomic DNA and genotyping. Total genomic DNA was purified from peripheral blood leukocytes using a DNA extraction kit of Puregene (Minneapolis, Minn., USA), following the manufacturer's protocol. The primers used for PCR amplification for the exon 2 of human *adiponectin* gene were: 5'-TAG AAG TAG ACT CTG CTG AGA TG-3' and 5'-CTC CCT GTG TCT AGG CCT TAG-3'. The PCR reactions were carried out in a total volume of 15 μ l containing 20 ng of genomic DNA with an initial denaturation at 94°C for 5 min, followed by denaturing at 94°C for 30 s, annealing at 68 to 60°C for 1 min with the annealing temperature stepping down 2°C for every five cycles, and polymerization at 72°C for 40 s; then by a final extension at 72°C for 10 min. Of the amplified DNA 4 μ l was digested with the *Bsp*HI enzyme (New England Biolabs, Beverly, Mass., USA), and then electrophoresed on a 2% agarose gel. The resulting fragment of PCR was 422 base pairs (bp). As the *T94G* substitution abolished a *Bsp*HI restriction site, two fragments of 265 and 157 bp after digestion indicated the presence of *T* allele. This polymorphism is equivalent to the SNP45 described elsewhere [16]. The genotyping of *PPAR* γ 2 *Pro12Ala* was published previously [9].

Statistical analyses. *Association analysis for adiponectin genotypes* — All variables were in SI units except that in HOMA_{IR}. The data were given in means and S.E. In order to compare each outcome variable between the *G* variant-carrying individuals (including the genotypes *T/G* and *G/G*) and their siblings with the genotype *T/T*, only the siblings with discordant genotypes in *T94G* polymorphism of the *adiponectin* gene were included in the analysis. Paired analysis was used to test whether there was difference in variables of interest between the siblings discordant for genotypes after adjustment for age, sex, BMI, ethnicity and area of enrollment by using analysis of covariance with these variables as covariates. The analyses were done using the SAS version 8.0 PROC GLM. We also carried out analysis of covariance using a mixed model to assess whether the *adiponectin* genotypes affect the outcome variables controlling for covariates age, sex, BMI, ethnicity and area of enrollment as fixed effects, and controlling for clustering among families as a random effect. The analyses were performed using the SAS 8.0 PROC MIXED. All statistical tests were two-tailed. A *p* value of less than 0.05 was considered statistically significant.

Analyses on adiponectin gene and *PPAR* γ 2 gene interactions. In order to assess the interactions between the *adiponectin* and *PPAR* γ 2 genotypes, we carried out an analysis of covariance using a mixed model to evaluate the contribution of the main effects of *adiponectin* *T49G* and *PPAR* γ 2 *Pro12Ala* respectively, and their interactions for each variable of interest in the same model controlling for covariates age, sex, BMI ethnicity and area of enrollment as fixed effects and entering family as a random effect. The analyses were done using the SAS 8.0 PROC MIXED.

Table 1. The proportions (%) and the numbers of subjects with specific *adiponectin* *T94G* genotypes and alleles among Chinese or Japanese subjects and hypertensive probands

		Genotypes			Alleles	
		<i>TT</i>	<i>TG</i>	<i>GG</i>	<i>T</i>	<i>G</i>
Subjects	Chinese	50.15%	39.77%	10.08%	70.04%	29.96%
		667	529	134	1863	797
	Japanese	50.28%	41.25%	8.47%	70.90%	29.10%
		273	224	46	770	316
Probands	All	47.83%	41.52%	10.65%	68.59%	31.41%
		265	230	59	760	348
	Chinese	47.90%	41.48%	10.62%	68.64%	31.36%
		194	168	43	556	254
	Japanese	47.65%	41.61%	10.74%	68.46%	31.54%
		71	62	16	204	94

Table 2. Characteristics of the subjects discordant for the *adiponectin* genotypes are compared in subjects with the *T/T* vs. those with the *T/G* or *G/G*

Variables	<i>T/T</i> (n=844) Means $\pm$ S.E.	<i>T/G</i> or <i>G/G</i> (n=869) Means $\pm$ S.E.	<i>p</i> **
Gender (male/female)	372/472	389/480	NS
Ethnicity (Chinese/Japanese)	619/225	631/238	NS
Area (Taiwan/San Francisco/Hawaii)	513/96/235	509/92/268	NS
Age (years)	50.78 $\pm$ 0.38	50.88 $\pm$ 0.38	NS
BMI (kg/m ²)	25.65 $\pm$ 0.16	25.96 $\pm$ 0.16	NS
Waist (cm)	85.71 $\pm$ 0.47	86.64 $\pm$ 0.47	NS
Waist to hip ratio	0.88 $\pm$ 0.00	0.89 $\pm$ 0.00	NS

** NS for *p*>0.1

The differences of several variables between the subjects with different *adiponectin* genotypes within fixed *PPAR* γ 2 genotypes after adjusting for age, sex, ethnicity, BMI, area of enrollment and family effects were compared. The values/bars reported are the least square means for each subgroup. The *p* values were obtained using the SAS 8.0 PROC MIXED. The SAS statistical program is from the SAS Institute (Cary, N.C., USA).

Results

The genotype and allele frequencies of *adiponectin* *T94G* polymorphism in Japanese and Chinese subjects were comparable (Table 1). The genotype and allele frequencies in the hypertensive probands were similar and did not deviate from Hardy-Weinberg equilibrium (Table 1). The genotype and allele frequencies, and the basic characteristics of these subjects categorized by the *PPAR* γ 2 genotypes were reported previously [9]. Using a sibling-based comparison for phenotypic variables, we found that the subjects with the *T/T* genotype (*n*=282) had higher mean plasma insulin concentration at 1 h (Ins60) during OGTT than that of the sibs with the discordant genotypes (*T/G* and *G/G*, *n*=312) after adjustment for age, sex, BMI, ethnicity and the area of enrollment (562 $\pm$ 27 vs. 483 $\pm$ 18

pmol/l, *p*=0.0067). The difference in the AUC_i in OGTT was of borderline statistical significance (828 $\pm$ 37 vs. 743 $\pm$ 27 pmol.h/l, *p*=0.0578). The differences between discordant *adiponectin* genotypes in the other variables did not reach statistical significance (data not shown).

To confirm the above findings, we also used a mixed model to correct for familial effects. This method enabled us to include more subjects for analyses. The basic characteristics of the subjects included in this analysis were shown in Table 2. After adjusting for age, sex, BMI, ethnicity and area of enrollment, only the means in Ins60 and AUC_i in OGTT were different between subjects with the *T/T* genotype and those otherwise (Table 3). Post-glucose load hyperinsulinaemia among subjects with the *T/T* genotype in order to normalize plasma glucose concentrations shown in these two analyses suggests that they could be more insulin resistant. We also carried out the analyses by categorizing the subjects into three *adiponectin* genotypes (*n*=844 of *T/T*, *n*=701 of *T/G* and *n*=168 of *G/G*). The results were quite similar, only the mean Ins60 (525 $\pm$ 18 vs. 455 $\pm$ 20 vs. 461 $\pm$ 35 pmol/l, *p*=0.0035) and AUC_i (785 $\pm$ 26 vs. 702 $\pm$ 28 vs. 719 $\pm$ 50 pmol.h/l, *p*=0.0204) were significantly different among the three genotypes. The differences were

Table 3. Comparisons of metabolic variables between subjects with discordant *adiponectin* genotypes after adjustment for age, sex, BMI, ethnicity and area of enrollment using a mixed model corrected for family effects

Variables*	<i>T/T</i> (<i>n</i> =844) Means $\pm$ S.E.	<i>T/G</i> or <i>G/G</i> (<i>n</i> =869) Means $\pm$ S.E.	<i>p</i> =***
Glu0	5.35 $\pm$ 0.05	5.31 $\pm$ 0.05	NS
Glu60	9.52 $\pm$ 0.14	9.35 $\pm$ 0.14	NS
Glu120	7.81 $\pm$ 0.14	7.71 $\pm$ 0.14	NS
AUCg	16.11 $\pm$ 0.21	15.86 $\pm$ 0.21	NS
Ins0	54.5 $\pm$ 1.5	53.4 $\pm$ 1.5	NS
Ins60	525.0 $\pm$ 18.4	455.9 $\pm$ 18.4	0.0008
Ins120	475.3 $\pm$ 20.0	447.1 $\pm$ 20.0	NS
AUCi	784.7 $\pm$ 26.3	705.2 $\pm$ 26.3	0.0056
HOMA _{IR} **	1.84 $\pm$ 0.06	1.84 $\pm$ 0.06	NS

*Abbreviations: Glu, plasma glucose at the specific time point in OGTT; Ins, plasma insulin at the specific time point in OGTT; AUCg, area under curve of plasma glucose in OGTT; AUCi, area under curve of plasma insulin in OGTT

** HOMA: homeostasis model assessment calculated by [Insulin/22.5e^{-ln}(Glucose)]

*** *p* values greater than or equal to 0.1 are marked NS (not significant), *p* values less than 0.05 are in bold

Table 4. Significance levels of the *adiponectin* or *PPAR* γ 2 genotypes on the main effects and their interactions after adjustment for age, sex, ethnicity, BMI, and area of enrollment using a mixed model corrected for family effects

Variables*	Adiponectin T94G Main effects		PPAR γ 2 Pro12Ala Main effects		Interactions	
	F(d.f.s)=**	<i>p</i> =	F(d.f.s)=	<i>p</i> =	F(d.f.s)=	<i>p</i> =
Glu0	3.61(1,811)	0.0671	0.36(1,811)	0.5491	2.96(1,811)	0.0859
Glu60	0.47(1,687)	0.4951	5.76(1,687)	0.0167	0.01(1,687)	0.9271
Glu120	0.37(1,715)	0.5459	2.47(1,715)	0.1167	0.09(1,715)	0.7640
AUCg	0.69(1,678)	0.4063	5.35(1,678)	0.0210	0.08(1,678)	0.7751
Ins0	4.72(1,808)	0.0301	0.41(1,808)	0.5243	4.81(1,808)	0.0285
Ins60	8.64(1,696)	0.0034	0.58(1,691)	0.4468	1.81(1,696)	0.1795
Ins120	5.54(1,722)	0.0189	0.68(1,722)	0.4083	4.09(1,722)	0.0435
AUCi	9.07(1,682)	0.0027	0.73(1,682)	0.3937	3.32(1,682)	0.0691
HOMA _{IR}	4.20(1,807)	0.0408	0.64(1,807)	0.4255	5.90(1,807)	0.0154

** F(d.f.s): F-value (degrees of freedom for the numerator and denominator of the relevant F statistics)

primarily between the *T/T* and the other two genotypes, suggesting a dominant effect of the *G* allele in association with insulin sensitivity. Thus this allowed us to pool *G/T* and *G/G* genotypes together in all the analyses. No significant difference among the three genotypes was observed in the other variables (data not shown).

Next we investigated the effects of genetic interactions between the *adiponectin* T94G and the *PPAR* γ 2 Pro12Ala polymorphisms. Previously, we found in the same study population that the *PPAR* γ 2 Ala12 variant was associated with better glucose tolerance at 0 (Glu0) and 1 h (Glu60) in OGTT and with lower insulin resistant index by HOMA (HOMA_{IR}) [9]. Using two-way ANOVA analysis, we found that there were significant interactions between the *adiponectin* and *PPAR* γ 2 genotypes in insulin concentrations at 0 (Ins0) and 2 h (Ins120) in OGTT and HOMA_{IR}, with adjustment for age, sex, BMI, ethnicity and area of enrollment, whereas their interactions in Glu0 and

AUCi were of borderline significance (Table 4). Interestingly, the main effects of *adiponectin* genotypes were all significant on every parameter (Ins0, Ins60, Ins120 and AUCi) of insulin in OGTT and HOMA_{IR}. The main effect of the *adiponectin* genotypes on Glu0 was of borderline significance (Table 4). In contrast, the main effects of *PPAR* γ 2 genotypes were only significant on Glu60 and area under curve of glucose (AUCg) in OGTT (Table 4).

To clearly illustrate the effects of interactions, these subjects were grouped by their genotypes. It was apparent that the subjects carrying both the *adiponectin* *G* and *PPAR* γ 2 Ala12 alleles were more insulin sensitive. They tended to have lower fasting plasma glucose and insulin, plasma insulin concentrations in OGTT, and HOMA_{IR} (Table 5, Fig. 1). Subjects with the *adiponectin* *G* allele even when coupled with *PPAR* γ 2 Pro/Pro still had lower insulin concentrations at 1 h and AUCi in OGTT than subjects with the *T/T* genotype (Table 5 and Fig. 1A).

Fig. 1. **A** Comparisons of AUC_i between the subjects with different combinations of the *adiponectin* and *PPAR* γ 2 genotypes, the bars show means $\pm$ S.E., * $p=0.0357$, ** $p=0.0118$. **B** Comparisons of AUC_g between the subjects with different combinations of the *adiponectin* and *PPAR* γ 2 genotypes, the bars showed means $\pm$ S.E. **C** Comparisons of HOMA_{IR} between the subjects with different combinations of the *adiponectin* and *PPAR* γ 2 genotypes, the bars showed means $\pm$ S.E., *** $p=0.0201$

Table 5. Comparisons between the subjects with different combinations of *adiponectin* and *PPAR* γ 2 genotypes. The p values in the 1st column from the right indicate the comparisons between the different *adiponectin* genotypes within a group with the same *PPAR* γ 2 genotypes. The p values at the bottom indicate the comparisons between the different *PPAR* γ 2 genotypes within a group with the same *adiponectin* genotypes

Variables	<i>PPAR</i> γ 2 genotypes	Adiponectin genotypes		$p=$
		T/T	G/-	
<i>n</i>	<i>Pro/Pro</i>	779	804	
	<i>Ala/-</i>	63	62	
Glu0	<i>Pro/Pro</i>	5.34 $\pm$ 0.05	5.33 $\pm$ 0.05	NS
	<i>Ala/-</i>	5.46 $\pm$ 0.15	5.08 $\pm$ 0.16	0.0649
$p=$		NS	NS	
Glu60	<i>Pro/Pro</i>	9.57 $\pm$ 0.14	9.41 $\pm$ 0.14	NS
	<i>Ala/-</i>	8.90 $\pm$ 0.38	8.69 $\pm$ 0.40	NS
$p=$		0.0833	0.0721	
Glu120	<i>Pro/Pro</i>	7.85 $\pm$ 0.14	7.76 $\pm$ 0.14	NS
	<i>Ala/-</i>	7.46 $\pm$ 0.39	7.21 $\pm$ 0.42	NS
$p=$		NS	NS	
AUC _g	<i>Pro/Pro</i>	16.18 $\pm$ 0.22	15.95 $\pm$ 0.21	NS
	<i>Ala/-</i>	15.27 $\pm$ 0.58	14.82 $\pm$ 0.61	NS
$p=$		NS	0.0618	
Ins0	<i>Pro/Pro</i>	54.2 $\pm$ 1.6	54.2 $\pm$ 1.5	NS
	<i>Ala/-</i>	59.1 $\pm$ 4.4	45.1 $\pm$ 4.7	0.0234
$p=$		NS	0.0554	
Ins60	<i>Pro/Pro</i>	519.3 $\pm$ 19.0	459.1 $\pm$ 18.9	0.0050
	<i>Ala/-</i>	599.8 $\pm$ 52.9	439.5 $\pm$ 55.3	0.0256
$p=$		NS	NS	
Ins120	<i>Pro/Pro</i>	467.0 $\pm$ 20.5	453.2 $\pm$ 20.5	NS
	<i>Ala/-</i>	479.5 $\pm$ 54.8	410.8 $\pm$ 58.6	0.0225
$p=$		0.0430	NS	
AUC _i	<i>Pro/Pro</i>	774.5 $\pm$ 27.1	711.8 $\pm$ 26.8	0.0357
	<i>Ala/-</i>	916.4 $\pm$ 74.3	665.8 $\pm$ 76.8	0.0118
$p=$		0.0605	NS	
HOMA _{IR}	<i>Pro/Pro</i>	1.83 $\pm$ 0.07	1.88 $\pm$ 0.07	NS
	<i>Ala/-</i>	2.04 $\pm$ 0.19	1.44 $\pm$ 0.20	0.0201
$p=$		NS	0.0294	

Discussion

In this report, we showed that the *adiponectin* T94G genotypes indeed were associated with the variation in insulin sensitivity, indicated indirectly by the serum insulin concentrations and insulin resistance index by HOMA (HOMA_{IR}), in a cohort of Chinese and Japanese hypertension families recruited in the Sapphire study. The subjects with the *T/T* genotype had higher post-glucose load insulin concentrations but similar glucose concentrations than those with the other genotypes, indicating insulin resistance associated with *T/T* genotypes. It should be noted that diabetic subjects were excluded in the recruitment of Sapphire study [10]. Compared with four recent population-based genetic association studies [15, 16, 17, 18], the advantage of the current study is that this is a family-based association study utilizing siblings as control subjects. As they share similar genetic and environmental backgrounds with the population control subjects, the ob-

served phenotypic differences between them are more likely the results of genetic differences in interest [11].

There has been a great interest in tackling the genetic make-up of human complex traits or diseases, such as diabetes, obesity and hypertension. Although a huge amount of genetic data has been accumulated in the past, not very many have addressed the issue of genetic interactions [4, 5]. To our knowledge, our study is one of the earliest to investigate the genetic interactions in connection with insulin resistance. Significant interactions between the genotypes of *adiponectin* and *PPAR* γ 2 in relation to fasting insulin and post-glucose load insulin concentration at 2 h and HOMA_{IR} were noted, providing some genetic evidence in humans that these two genes could participate either in the same pathway or in two interdependent pathways related to the biological processes of insulin sensitivity. Consistent with this, previous studies in cell culture, in animals and in humans have shown that *adiponectin* expression either at mRNA or at protein levels could be up-regulated by *PPAR* γ 2 activation [21, 22, 23, 24, 25]. This study has shown that a genetic association study is capable of detecting genetic epistasis.

The molecular mechanisms behind the genetic interactions between *adiponectin* and *PPAR* γ 2 genotypes are not clear. The *T94G* polymorphism of *adiponectin* is a silent mutation for Gly15 (GGT to GGG). We speculated that it might be in linkage disequilibrium with the other genetic alterations, probably a regulatory mutation. In contrast, the *PPAR* γ 2 *Ala12* variant was previously shown to have reduced transactivating ability [8]. Although only a half-site of *PPAR* γ response element (PPRE) was recognized in the proximal promoter of *adiponectin* by sequence analysis, synthetic *PPAR* γ 2 agonists were shown to enhance transcription of luciferase driven by the proximal 2 kb of *adiponectin* promoter [23]. How *PPAR* γ 2 variants might activate the *adiponectin* gene in different promoter contexts is an important question to address in the future.

In conclusion, we found that the *T94G* polymorphism of the *adiponectin* gene was associated with insulin sensitivity, represented by serum insulin levels and HOMA_{IR} , in the subjects from a large hypertensive family cohort. More importantly, the effect of *adiponectin* was modified by the *PPAR* γ 2 *Pro12Ala* genotypes, indicating a genetic interaction in association with insulin sensitivity. These observations suggest that both the *adiponectin* and *PPAR* γ 2 genes and the interactions between them could play a role in the etiopathogenesis of insulin resistance.

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