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Metabolism Clinical and Experimental 54 (2005) 1552–1556

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

The C161→T polymorphism in peroxisome proliferator–activated receptor gamma, but not P12A, is associated with insulin resistance in Hispanic and non-Hispanic white women: evidence for another functional variant in peroxisome proliferator–activated receptor gamma

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Received 31 March 2005; accepted 10 May 2005

Abstract

The P12A variant in the peroxisome proliferator–activated receptor gamma (PPARγ) gene has been intensely studied for association with obesity-related or type-2 diabetes–related traits; however, the results have been somewhat inconsistent in different populations. We genotyped a large cohort of Hispanic and non-Hispanic white individuals from the San Luis Valley Diabetes Study for P12A and another common variant, C161→T, in the PPARγ gene to determine if these sites were associated with fasting glucose, insulin, free fatty acid levels, insulin sensitivity, or body fat. There were no statistically significant frequency differences at these two sites between Hispanic and non-Hispanic individuals. No significant association with the metabolic phenotypes was observed for either of the polymorphisms in men; however, in women, significant associations were shown between the C161→T variant and fasting insulin (P = .008) and the homeostasis model assessment of insulin resistance (HOMA IR; P = .007). After adjusting for age, smoking, fat mass, and skin reflectance, linear regression showed that C161→T explained 1.5% of the variation in both fasting insulin (P = .031) and HOMA IR (P = .028) whereas P12A contributed only 0.04% (fasting insulin, P = .268) and 0.02% (HOMA IR, P = .418) to the total trait variation. In the San Luis Valley Diabetes Study female patients, C161→T appears to be a better predictor of fasting insulin levels and insulin resistance than P12A although the effect of this variant is small. These results support the hypothesis that C161→T is in linkage disequilibrium with unidentified functional variation in PPARγ or in a linked gene. This could explain some of the inconsistencies in the P12A association studies as the allele frequency and level of linkage disequilibrium of another functional polymorphism in the region could vary in different populations.

1. Introduction

Peroxisome proliferator–activated receptors (PPARs) regulate a number of cellular functions related to lipid metabolism, glucose homeostasis, and adipocyte differentiation. The PPARγ gene is located on chromosome 3 and consists of two 5′ untranslated exons, a 5′ exon specific for the γ2 isoform that codes for an additional 28 amino acids, and 6 coding exons shared among all PPARγ isoforms [1-3]. Of the 4 known PPARγ isoforms, PPARγ1, PPARγ3, and PPARγ4 have identical mature proteins and are expressed in several tissues including the adipose tissue, liver, muscle, and heart [4,5]. The PPARγ2 isoform, with its unique first exon, is regulated by an independent promoter and is only expressed at low levels in adipocytes and possibly in the liver or skeletal muscle cells [6]. The PPARγ activators include fatty acids, fatty acid derivatives, and synthetic compounds such as the thiazoladinediones, which are drugs used to improve insulin sensitivity [7,8].

Rare inactivating mutations in PPARγ have been shown to cause severe monogenic forms of obesity or insulin

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doi:10.1016/j.metabol.2005.05.025

Table 1
Genotype counts for PPARγ polymorphisms in the San Luis Valley Diabetes Study population

Polymorphic site	Hispanics			Non-Hispanics			*P*
	11	12	22	11	12	22	
P12A (C/G)	229	60	4	322	86	6	.991
C161→T (C/T)	218	61	3	301	105	11	.168

resistance with dyslipidemia and hypertension [9,10]. Two common polymorphisms, a silent C to T transversion in exon 6 (C161→T; rs3856806) and a C (proline) to G (alanine) substitution at codon 12 (P12A; rs3856806), have been reported in PPARγ [11]. There is evidence to suggest that the mutant protein produced by the alanine allele at codon 12 has reduced transcriptional and adipogenic activity in vitro, which could lead to lower adipose tissue mass [12]. In addition, the alanine allele was found to be associated with lower rates of lipolysis and greater insulin sensitivity in a group of lean nondiabetic subjects [13].

The C161→T polymorphism in exon 6 has been associated with high-density lipoprotein cholesterol, leptin levels, and reduced risk for coronary artery disease [14-16]. Valve et al [17] examined the P12A and C161→T variants and found that both polymorphisms were associated with several measures of obesity among obese women, but P12A showed a stronger association than C161→T. In separate studies, the alanine allele at P12A has been reported to be associated with increased body mass index (BMI) [18-20] and decreased BMI [21] compared with the proline allele. Ek et al [22] found that the alanine allele was related to higher BMI in a sample of obese Danish men but lower BMI in the nonobese control subjects, suggesting that its effect may be weight dependent. In a study of 16 common single nucleotide polymorphisms previously reported to influence diabetes risk, P12A was the only polymorphism to show a reproducible association between the alanine allele and decreased diabetes risk among Scandinavians [23]. On the other hand, a study of the Canadian Oji-Cree found that the alanine allele of the P12A polymorphism was associated with increased risk for type-2 diabetes in women but not in men [24]. Thus, it is likely that the P12A variant either functions/behaves differently among distinct ethnic groups or environments or is in varying linkage disequilibrium with another polymorphism that is also influencing measures of obesity or diabetes. The purpose of this study was to evaluate the association of both the P12A and C161→T variants on measures of obesity and diabetes in a large biethnic population from southern Colorado.

2. Methods

2.1. Subjects

The San Luis Valley Diabetes Study is a geographically based case–control study designed to identify risk factors for type-2 diabetes, heart disease, and obesity in a population of Hispanic and non-Hispanic white individuals living in southern Colorado. Metabolic, anthropometric, and interview data were collected over the course of 3 possible visits in a 14-year period. The 764 individuals included in this study participated in the third clinic visit and were not diabetic at the baseline visit based on World Health Organization criteria [25]. Informed consent was obtained from all subjects and the University of Colorado Health Sciences Center Institutional Review Board approved all protocols. A more detailed description of this population can be found in the work of Hamman et al [26].

Fat mass was measured by dual energy X-ray absorptiometry using a LUNAR DPX-L scanner (Lunar Corp, Madison, Wis) [27]. Serum levels of free fatty acids, glucose, and insulin were measured from blood samples after an 8- to 12-hour fast. The homeostasis model assessment of insulin resistance (HOMA IR) was used as a measure of insulin resistance [HOMA IR = (fasting insulin × fasting glucose)/22.5] [28]. Skin reflectance measured by a portable spectrophotometer was used as a surrogate for ethnicity to account for admixture [29]. Smoking status was classified in two categories: nonsmokers vs current and ex-smokers.

2.2. Genotyping

Both of the PPARγ variants were amplified using standard polymerase chain reaction conditions and genotyped by restriction enzyme digestion. The P12A polymorphism was detected through an engineered *Bst*UI restriction enzyme site [11]. The C161→T variant was amplified with primers $^{5'}$gatgagttgcttggtagagctg$^{3'}$and $^{5'}$cgggtgaagactcatgtctgt$^{3'}$ and genotyped by digestion with *Nla*III. The digested DNA

Table 2
Genotype means (SD) for P12A and C161→T vs outcome variables adjusted for skin reflectance in women

	P12A			C161→T		
	CC	CG or GG	*P*	CC	CT or TT	*P*
Fasting glucose (mg/dL)	97 (21)	97 (15)	.986	98 (22)	94 (11)	.100
Fasting insulin (mg/dL)	11.5 (7.3)	10.0 (5.7)	.084	11.7 (7.4)	9.5 (5.0)	.008
HOMA IR	17.9 (14.9)	15.3 (11.5)	.131	18.4 (15.3)	13.8 (8.6)	.007
Free fatty acids (μmol/L)	662 (245)	661 (236)	.967	663 (237)	653 (253)	.729
Percent fat (%)	42.1 (7.2)	41.3 (7.6)	.438	42.2 (7.1)	41.0 (8.0)	.185
Fat mass (kg)	29.2 (9.7)	29.0 (10.1)	.510	29.4 (9.8)	27.8 (10.0)	.191
n	271	84		244	86	

fragments were resolved on a 2% agarose gel and visualized under UV light in the presence of ethidium bromide.

2.3. Statistical analysis

Allele frequencies were estimated for all typed polymorphisms. Fit to the expectations of Hardy-Weinberg equilibrium was tested by the χ^2 test. Ethnic differences in genotype frequencies were also tested using a χ^2 test. The EH program was used to estimate haplotype frequencies with association that were then used to estimate linkage disequilibrium (D') between the two sites [30-32]. Because of the small number of individuals homozygous for the less common allele at each locus, these individuals were combined with the heterozygous subjects for all further analyses.

All other statistical analyses were done using SPSS statistical analysis software version 10.0 for Macintosh (SPSS, Chicago, Ill). Adjusted dependent variables were calculated using linear regression to determine the unstandardized residuals then by adding back the mean of the unadjusted outcome. Student's t test was then used to test the effect of each polymorphism on dependent variables adjusted for skin reflectance. Separate models were tested for men and women.

Next, regression models were constructed for the traits showing association with at least one of the polymorphisms in the earlier analysis (fasting insulin and HOMA IR). These variables were adjusted for skin reflectance, fat mass, smoking, and age using the method described earlier. Models using the adjusted dependent variables were tested to determine the effect of each variant alone and in combination. Separate models were tested for P12A alone, C161→T alone, and both sites together plus their interaction.

3. Results

Allele frequencies were calculated for each of the polymorphisms in both ethnic groups. There were no statistically significant deviations from Hardy-Weinberg equilibrium. The frequencies of the less common alleles at both sites were similar in the two ethnic groups (P12A, q = .116 for Hispanics and q = .118 for non-Hispanics; C161→T, q = .118 for Hispanics and q = .152 for non-Hispanics). There was no statistically significant difference between the genotype frequencies in the two ethnic groups (see Table 1). The two PPARγ variants were in linkage disequilibrium in both ethnic groups (D' = .873 for Hispanics; D' = .688 for non-Hispanics).

Table 3
Regression models for ln(fasting insulin) [mg/dL] vs P12A and C161→T in women

Models	β	P	Constant	r^2
P12A	−.065	.268	2.224	.004
C161→T	−.123	.031	2.240	.015
P12A	.114	.347		
C161→T	−.109	.285	2.233	.018
Interaction	−.122	.461		

Table 4
Regression models for ln(HOMA IR) vs P12A and C161→T in women

Models	β	P	Constant	r^2
P12A	−.057	.418	2.577	.002
C161→T	−.150	.028	2.602	.015
P12A	.188	.193		
C161→T	−.161	.188	2.590	.021
Interaction	−.158	.426		

To determine the effect of each of the polymorphisms in the PPARγ gene, P12A and C161→T were tested for associations with several obesity-related or type-2 diabetes–related phenotypes (fasting glucose, fasting insulin, HOMA IR, fasting free fatty acids, percent body fat, and fat mass) after adjusting for skin reflectance. No significant association was observed for either of the polymorphisms in men. In women, the C161→T variant showed significant association with fasting insulin (P = .008) and HOMA IR (P = .007). Table 2 shows the genotype means for each of the outcome variables in women. Presence of the T allele at the C161→T site was associated with 2.2 mg/dL lower fasting insulin levels as compared with female CC homozygotes. Similarly, mean HOMA IR levels were almost 5 U lower in carriers of the T allele as compared with CC individuals. A similar trend was apparent for the association of the P12A polymorphism with fasting insulin and HOMA IR but was not significant. Associations between the PPARγ variants and obesity-related or type-2 diabetes–related phenotypes were also tested in each ethnic group separately. These results were similar to the results when both ethnic groups were considered together and adjusted for skin reflectance (data not shown). Because of the small sample sizes when the ethnic groups were analyzed separately, the women were considered together and skin reflectance was used as a covariate in subsequent analyses.

After adjusting for age, smoking, fat mass, and skin reflectance, linear regression analysis showed that the C161→T site was a significant predictor of fasting insulin and HOMA IR whereas P12A was not. Models were estimated for each polymorphism alone and for both sites plus their interaction. The P12A models were not significant and only explained 0.02% (HOMA IR) to 0.04% (fasting insulin) of the adjusted trait variation. Both models with only C161→T accounted for 1.5% of the variation in adjusted fasting insulin (P = .031) or adjusted HOMA IR (P = .028). No significant interaction between the two sites was observed for either fasting insulin or HOMA IR (see Tables 3 and 4).

4. Discussion

Given that the P12A and C161→T variants are in linkage disequilibrium and that C161→T is a silent substitution and likely nonfunctional, it is possible that C161→T is merely a marker for P12A. However, P12A, as the potentially

functional polymorphism, would be expected to be a better predictor of any associated trait. Analysis of these two polymorphisms in the San Luis Valley Diabetes Study revealed that the T allele of C161→T is associated with significantly lower fasting insulin levels and HOMA IR in women. This effect was modest (2.2 mg/dL for fasting insulin and 4.6 U for HOMA IR) and was highly significant (P = .008 and P = .007, respectively). This association was still present after adjustment for age, smoking, fat mass, and skin reflectance (P = .031 for fasting insulin and P = .028 for HOMA IR). Moreover, the C161→T variant explained a greater amount of variation in these traits than did P12A (r^2 = .015 for C161→T vs $r^2 \approx$ .003 for P12A). P12A was not significantly associated with any of the measures of obesity and type-2 diabetes that were tested and no significant interaction between the two sites was observed.

Two prior studies have reported the PPARγ locus to have a stronger effect in women than in men. Beamer et al [18] found that the alanine allele of P12A was associated with several measures of obesity and that the effect was most prominent in obese women. Another study that examined both sites in PPARγ found that P12A was a better predictor of adiposity in obese women than was C161→T [17]. However, the same study did find evidence of an interaction between these sites by observing that there was a greater difference in BMI and fat mass between the common and rare double homozygous individuals as compared with the difference in homozygous individuals when the polymorphisms were considered separately.

The PPARγ2 isoform makes up approximately 10% to 15% of the total PPARγ messenger RNA expression in human adipose tissue [6]. However, the ratio of PPARγ1 to PPARγ2 messenger RNA seems to vary between individuals [33]. Vidal-Puig et al [4] found that the ratio of PPAR γ2 to PPAR γ1 was correlated with BMI and that women showed increased expression of both isoforms. This supports the idea that the effect of genetic variation in PPARγ would be more pronounced in women or obese subjects. It also seems likely that genetic variation affecting all 4 of the PPARγ isoforms would have a large effect on PPARγ-related traits because the P12A polymorphism, which is only present in the uncommon PPARγ2 isoform, has been associated with risk for type 2 diabetes [34].

The results from the current study in combination with the findings from other groups suggest the possibility that C161→T is marking another functional variant in the PPARγ gene region other than the frequently studied P12A variant. This possibility has already been proposed by Hegele et al [24], who found that the G (alanine) allele for P12A was associated with increased susceptibility to type-2 diabetes in a Canadian Indian population, which conflicted with the findings of many other studies. Comprehensive screening of the entire PPARγ gene region, especially the 4 identified promoter regions, is necessary to ensure that all common variations in this region have been identified.

In the San Luis Valley population, C161→T appears to be a better predictor than P12A of fasting insulin levels and insulin sensitivity although the effect of this variant is modest. The reduction in fasting insulin and HOMA IR levels is not likely to be caused by the potentially protective nature of the alanine allele because P12A itself was not an important predictor for these traits. If P12A were the functional site influencing these traits, then it would have demonstrated a greater association than the C161→T. This supports the hypothesis that C161→T is in linkage disequilibrium with another unidentified functional variation in PPARγ or in a linked gene. If true, this could help explain some of the inconsistencies in the PPARγ association studies as the allele frequency and level of linkage disequilibrium with other functional variation in the region could vary between populations.

Acknowledgment

This work was supported by NIH grants DK46204 and DK30747. We thank the residents of San Luis Valley, Colo, for participating in this study. Susan P. Moffett was supported by NIA T32 AG00181-13.

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