POLYMORPHISMS IN THE ADIPONECTIN GENE AND RESPONSE TO PIOGLITAZONE

The goal of this study was to genotype single nucleotide polymorphism (SNP) 45 and SNP276 in participants in the Pioglitazone of the Prevention of Diabetes study. We genotyped each SNP by using allelic discrimination in 93 non-diabetic Hispanic women (63 responders, 30 nonresponders) with previous gestational diabetes but did not find evidence for association between these variants and pioglitazone response, which was defined as the lower tertile in change in insulin sensitivity after three months of treatment. The discrepancy between the present findings and the previously reported study may be due to ethnic differences, differential drug effects, or study design.

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INTRODUCTION

Pioglitazone in the Prevention of Diabetes (PIPOD) was a placebo-controlled intervention study that compared the effects of pioglitazone and placebo on type 2 diabetes rates, insulin resistance, and β-cell function in women with previous gestational diabetes mellitus. Pioglitazone belongs to the class of drugs called thiazolidinediones, which are agonists for the peroxisome proliferator-activated receptor-γ. Among the women in the PIPOD treatment arm, diabetes incidence was reduced by 55%. However, >30% of the women who received pioglitazone did not respond to the drug and had a rate of diabetes similar to that in the placebo group. Since diabetes and insulin sensitivity have a genetic component, we hypothesized that individual response to pioglitazone treatment may also have genetic determinants. Because variation in the adiponectin gene (ACDC) has been previously reported to contribute to rosiglitazone response in Koreans with type 2 diabetes, we assessed the role of this gene in Hispanic women with previous gestational diabetes mellitus.

METHODS

We genotyped single nucleotide polymorphism (SNP) 45 and SNP276 by allelic discrimination with the ABI 7000 Sequence Detection System according to the manufacturer's instructions (Applied Biosystems, Foster City, Calif). Primers and probes were purchased as predesigned ABI Taqman SNP Genotyping assays (Applied Biosystems). The two variants were genotyped in 93 nondiabetic Hispanic women (63 responders, 30 nonresponders) from the PIPOD study. Association with pioglitazone response, defined as the lower tertile in change in insulin sensitivity after three months of treatment, was assessed by chi-square test, assuming dominant, recessive, and additive models. Data quality of the resulting genotypes was assessed by encrypted duplicates.

RESULTS

Table 1 shows the characteristics of the study participants on the basis of response to pioglitazone. Significant differences were seen between

Table 1. Baseline characteristics in study participants

	Responders *N*=63		Nonresponders (*N*=30)		
Baseline Phenotype	**Median**	**Q Range****	**Median**	**Q Range**	***P* value***
Age	41.34	7.48	37.84	9.96	.03
Weight (kg)	72.05	12.95	70.00	12.27	.51
Waist-hip ratio	.86	.08	.87	.09	.90
BMI (kg/m^2)	30.16	4.74	29.92	5.04	.72
Systolic blood pressure (mm Hg)	109.25	18.00	111.25	15.50	.83
Diastolic blood pressure (mm Hg)	71.25	11.25	69.00	13.00	.53
Insulin sensitivity	1.42	1.31	2.37	2.30	.008
Fasting glucose (mg/dL)	95.00	21.00	90.00	16.00	.06
Fasting insulin (mU/dL)	13.00	11.50	12.00	10.00	.40

BMI=body mass index

the two groups in age and insulin sensitivity.

To determine the extent to which the previously reported ACDC SNPs contributed to pioglitazone response in Hispanic women of the PIPOD study, we genotyped SNP45 and SNP276 in this population. The minor allele frequencies for SNP45 and SNP276 were .18 and .28, respectively. We first assessed the amount of linkage disequilibrium between SNP45 and SNP76; r^2, which is a measure of concordance (ie, absolute values of one only occur when complete linkage disequilibrium occurs and when the associated alleles have identical frequencies) was .08. In analyses of association, the variant G allele of SNP45 was not associated with pioglitazone response (odds ratio [OR]=.70, P=.45). Similarly, the variant T allele of SNP276 was not associated with pioglitazone response (OR=1.34, P=.45).

DISCUSSION

In this study, we did not confirm previous findings of association reported in Korean individuals. This discrepancy in results may be due to the possibility that different genetic variants underlie response in different populations; alternatively, ACDC SNPs may affect response to rosiglitazone but not pioglitazone. Finally, different study designs (ie, the Korean study looked at people with type 2 diabetes, whereas the present study included only individuals who were at risk for developing diabetes but were not diabetic) may underlie the disparities in the results between the two studies.