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Evidence for an association with type 2 diabetes mellitus at the *PPARG* locus in a South Indian population

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Abstract

Peroxisome proliferator–activated receptor–γ2 (PPARG2) is a nuclear hormone receptor of ligand-dependent transcription factor involved in adipogenesis and a molecular target of the insulin sensitizers thiazolidinediones. We addressed the question of whether the 3 variants (−1279G/A, Pro12Ala, and His478His) in the *PPARG2* gene are associated with type 2 diabetes mellitus and its related traits in a South Indian population. The study subjects (1000 type 2 diabetes mellitus and 1000 normal–glucose-tolerant subjects) were chosen randomly from the Chennai Urban Rural Epidemiology Study, an ongoing population-based study in southern India. The variants were screened by single-stranded conformational variant, direct sequencing, and restriction fragment length polymorphism. Linkage disequilibrium was estimated from the estimates of haplotypic frequencies. The −1279G/A, Pro12Ala, and His478His variants of the *PPARG2* gene were not associated with type 2 diabetes mellitus. However, the 2-loci analyses showed that, in the presence of Pro/Pro genotype of the Pro12Ala variant, the −1279G/A promoter variant showed increased susceptibility to type 2 diabetes mellitus (odds ratio, 2.092; 95% confidence interval, 1.22-3.59; $P = .008$), whereas in the presence of 12Ala allele, the −1279G/A showed a protective effect against type 2 diabetes mellitus (odds ratio, 0.270; 95% confidence interval, 0.15-0.49; $P < .0001$). The 3-loci haplotype analysis showed that the *A-Ala-T* (−1279G/A-Pro12Ala-His478His) haplotype was associated with a reduced risk of type 2 diabetes mellitus ($P < .0001$). Although our data indicate that the *PPARG2* gene variants, independently, have no association with type 2 diabetes mellitus, the 2-loci genotype analysis involving −1279G/A and Pro12Ala variants and the 3-loci haplotype analysis have shown a significant association with type 2 diabetes mellitus in this South Indian population.

1. Introduction

Diabetes is a major clinical and public health problem within certain racial and ethnic groups where both new cases of diabetes and the risk of associated complications are increasing at an alarming rate [1]. Indians are one such ethnic group who is considered to be a high-risk population for diabetes. Studies have shown that type 2 diabetes mellitus occurs at least 2 decades earlier in migrant Indians compared with the host population of those countries [2,3]. It is also well established that Asian Indians have greater insulin resistance [4] and waist -hip ratio [5,6], and increased susceptibility to diabetes [7-9] and to premature coronary artery disease [10,11] compared with Europeans. This is indicative of a strong genetic predisposition to type 2 diabetes mellitus and its related traits in Asian Indians.

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Peroxisome proliferator–activated receptor–γ2 (PPARG2) plays a significant role in regulating adipose cell differentiation and insulin action [12,13]. In addition to its role in adipogenesis, PPARG2 has a role in insulin signaling [14], insulin resistance [15], and development of type 2 diabetes mellitus [15] and is the target for the thiazolidinedione group of drugs. The relative potency of most thiazolidinediones to bind and activate PPARG2 in vitro correlates perfectly with their antidiabetic potency in vivo, suggesting that PPARG2 mediates their antidiabetic effect [16]. Because of its key role in adipogenesis and the expression of genes that favor energy storage, it has been called the *ultimate thrifty gene* [17].

In the present study, we screened the promoter and the coding regions of the *PPARG2* gene for novel variations and evaluated the association of the identified variants with type 2 diabetes mellitus and its metabolic abnormalities. Nine variants were identified, of which the highly prevalent *C*CA-to-*G*CA (Pro12Ala), the silent CAC478-CAT (His478His), and the promoter −1279G/A variants were considered for an extensive study on a large population based on location (promoter and coding region) and frequency. We have already shown in our earlier study that the Pro12Ala variant is not associated with type 2 diabetes mellitus in Asian Indians [18]. Recently, we have shown that Pro12Ala, His478His, and −1279G/A variants were not associated with metabolic syndrome in our population [19]. In this study, we examined the association of the 3 variants with type 2 diabetes mellitus and the combined effect of Pro12Ala with the other 2 variants in association with type 2 diabetes mellitus in a South Indian population.

2. Subjects and methods

2.1. Study population

A total of 2000 unrelated subjects were randomly selected from the Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiologic study conducted on a representative population of 26 001 individuals (aged ≥20 years) in Chennai (formerly Madras), the fourth largest city in India, with a population approximately of about 4.2 million. The methodology of the study has been described elsewhere [20]. In phase 1 of CURES, individuals were screened by a systematic sampling technique. In phase 2, all known diabetic subjects were invited to undergo oral glucose tolerance tests that were conducted using 75-g glucose load. Those who had fasting plasma glucose less than 5.6 mmol/L (100 mg/dL) and 2-hour plasma glucose value less than 7.7 mmol/L (139 mg/dL) were categorized as having normal glucose tolerance (NGT) [21]. Those who were confirmed by oral glucose tolerance tests to have 2-hour plasma glucose values of at least 11.1 mmol/L (200 mg/dL), based on the World Health Organization consulting group criteria, were labeled as "newly detected diabetic subjects." From this study, we randomly selected 1000 unrelated type 2 diabetes mellitus and 1000 NGT subjects for the current study. None of the subjects recruited for the study were on any lipid-lowering drugs. Informed consent was obtained from all study subjects, and the protocol was approved by the institutional ethics committee.

2.2. Measurement of clinical and biochemical variables

Anthropometric measurements including weight, height, and waist measurements were obtained using standardized techniques. The body mass index (BMI) was calculated using the formula weight (in kilograms)/height (in square meters). Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mm Hg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart, and the mean of the 2 was taken as the blood pressure.

Fasting plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method), and high-density lipoprotein cholesterol (direct method polyethylene glycol–pretreated enzymes) were measured using Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). The intra- and interassay coefficient of variation for the biochemical assays ranged between 0.04 to 0.08. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Glycated hemoglobin was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA). The intra- and interassay coefficient of variation of glycated hemoglobin was less than 10%. Serum insulin concentration was estimated using Dako kits (Dako, Glostrup, Denmark). The intra- and the interassay coefficients of variation for insulin assay were 0.06 and 0.09, respectively; and the lower detection limit was 0.5 μIU/mL. Insulin resistance was calculated using the homeostasis model assessment (HOMA) using the following formula: fasting insulin (in micro–international units per milliliter) × fasting glucose (in millimoles per liter)/22.5. Subjects whose HOMA insulin resistance values were greater than the fourth quartile for the nondiabetic population (ie, >2.58) were considered to have insulin resistance.

2.3. Molecular genetic analyses

Genomic DNA was isolated from the whole blood by the phenol-chloroform method. As a pilot screening, the promoter and the coding regions of the *PPARG2* gene were screened for novel variants in 500 subjects (250 type 2 diabetes mellitus and 250 NGT subjects) using single-stranded conformational polymorphism assay (SSCP) and sequencing on ABI310 sequencer (Applied Biosystems, Foster City, CA). Nine variants were identified, out of which only the common 3 variants were chosen for genotyping on 2000 subjects by polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP). The

methodology for detecting the Pro12Ala and His478His variants is published elsewhere [22]. The primers used to detect the −1279G/A variant were as follows: forward, 5′-TGCCATCGTGTCTGGATTAC-3′ and reverse, 5′-CCTGTCAATCATGGTGC AAG-3′. The PCR product was digested with *Nla*III (New England Biolabs, Ipswich, MA), and the RFLP products were resolved on a 3% agarose gel electrophoresis. To ensure that the genotyping was of adequate quality, we performed random duplicates in 20% of the samples and found 100% concordance in genotyping.

2.4. Statistical analysis

Statistical Package for Social Sciences for Windows, version 10.0 (SPSS, Chicago, IL), was used for statistical analysis. The effects of the variants on quantitative and categorical variables were analyzed. Allele frequencies were estimated by gene counting. Agreement with Hardy-Weinberg expectations was tested using a χ^2 goodness-of-fit test. Because of the small number of homozygotes in the study, individuals homozygous and heterozygous for *PPARG2* variants were grouped together for statistical analyses. Comparison of the means between the 2 groups was analyzed by Student *t* test. The χ^2 test was used to compare the proportions of genotypes or alleles. Logistic regression analysis was used to identify the risk of the genotype combinations for type 2 diabetes mellitus. Haplotype frequencies were estimated using an expectation-maximization algorithm, which equates each genotypic frequency to the sum of the probabilities of all possible haplotypic configurations resulting in that genotype. Linkage disequilibrium was estimated from the estimates of haplotypic frequencies. A P value < .05 was considered statistically significant. Significant P values obtained were corrected for multiple testing (Bonferroni correction).

3. Results

The diabetic subjects (52 ± 11 years) were older compared with the NGT subjects (46 ± 12 years, $P = .0001$). Compared with the NGT subjects, the diabetic subjects had significantly higher BMI (diabetes, 26.1 ± 4.2 kg/m^2 vs NGT, 24.0 ± 4.7 kg/m^2; $P = .003$), waist circumference (diabetes, 92.3 ± 9.4 cm vs NGT, 87.2 ± 11.4 cm; $P = .002$), total cholesterol (diabetes, 201 ± 42 mg/dL; NGT, 176 ± 37 mg/dL; $P < .0001$), and serum triglycerides (diabetes, 180 ± 130 mg/dL; NGT, 112 ± 65 mg/dL; $P < .0001$).

In the pilot screening, we identified 7 promoter (−2965C/T, −1515C/T, −1279G/A, −912C/T, −820G/A, −795T/C, and −62G/A) and 2 exonic (Pro12Ala[C/G] and His478His[C/T]) variants by SSCP and direct sequencing on 500 subjects. Out of these 9 variants, only 3 were frequent (>5%) in the population; and these 3 were genotyped on a larger population of 2000 subjects (1000 NGT and 1000 type 2 diabetes mellitus subjects) by PCR-RFLP. All the genotype frequencies of the 3 variants in subjects with type 2 diabetes mellitus and NGT were in Hardy-Weinberg equilibrium.

3.1. −1279G/A variant and type 2 diabetes mellitus

The genotype and allele frequencies of −1279G/A variant are shown in Table 1. The frequencies of the A allele in the NGT and type 2 diabetes mellitus subjects were not significantly different (0.08 and 0.07, $P = .284$). None of the clinical and biochemical parameters were statistically significant between the genotypes of −1279G/A variant.

3.2. Pro12Ala variant and type 2 diabetes mellitus

The genotype ($P = .601$) and the allele ($P = .518$) frequencies of the Pro12Ala variant were not statistically significant between NGT and type 2 diabetes mellitus subjects (Table 1). Genotype-phenotype study revealed that there was no difference in BMI, waist circumference, plasma insulin, insulin sensitivity index by HOMA model, fasting serum cholesterol, fasting serum triglycerides, and systolic and diastolic blood pressure between subjects with and without the Pro12Ala variant.

3.3. His478His (C/T) variant and type 2 diabetes mellitus

As shown in Table 1, distributions of genotype ($P = .545$) and relative allele ($P = .309$) frequencies of His478His (C/T) variant were not statistically significantly different between type 2 diabetes mellitus and NGT subjects. None of the clinical and biochemical profiles were significantly different

Table 1
Genotype and allele frequencies of the 3 variants in the *PPARG2* gene

Variants and their genotypes	NGT subjects	Type 2 diabetes mellitus subjects	*P* value
−1279G/A variant			
GG	840 (84.0%)	860 (86.0%)	
GA	157 (15.7%)	136 (13.6%)	.209 (2*2)
AA	3 (0.3%)	4 (0.4%)	.974 (2*2)
XA (GA + AA)			
Total	1000	1000	.389 (3*2)
MAF *(A)*	0.08	0.07	.284
Pro12Ala variant			
Pro/Pro	810 (81.0%)	820 (82.0%)	
Pro/Ala	183 (18.3%)	176 (17.6%)	.703 (2*2)
Ala/Ala	7 (0.7%)	4 (0.4%)	.535 (2*2)
X/Ala (Pro/Ala + Ala/Ala)			
Total	1000	1000	.601 (3*2)
MAF *(Ala)*	0.10	0.09	.518
His478His variant			
CC	780 (78.0%)	800 (80.0%)	
CT	212 (21.2%)	193 (19.3%)	.310 (2*2)
TT	8 (0.8%)	7 (0.7%)	.963 (2*2)
XT (CT + TT)			
Total	1000	1000	.545 (3*2)
MAF *(T)*	0.11	0.10	.309

MAF indicates minor allele frequency.

between CC and XT (CT + TT) genotypes of His478His variant among the NGT group.

3.4. Two-loci analysis

The initial analyses of this work necessitated a test for 2-loci analyses between the variants to look for any possible combined effects of these variants on the susceptibility to type 2 diabetes mellitus. Two-loci analyses between the variants −1279 G/A and His478His and the variants Pro12Ala and His478His did not reveal any significant association with type 2 diabetes mellitus (data not shown). However, the 2-loci analysis between the variants −1279G/A and Pro12Ala revealed a significant combined effect on type 2 diabetes mellitus. For this analysis, the study subjects were stratified into 2 groups based on the genotypes of Pro12Ala variant: Pro/Pro and X/Ala (Pro/Ala + Ala/Ala). In the presence of Pro/Pro genotype, the −1279G/A variant showed an increased susceptibility to type 2 diabetes mellitus after adjusting for age, sex, and BMI (odds ratio [OR], 2.092; 95% confidence interval [CI], 1.22-3.59; $P = .008$), whereas in the presence of 12Ala allele, the −1279 G/A variant showed a protective effect against type 2 diabetes mellitus (adjusted OR, 0.270; 95% CI, 0.15-0.49; $P < .0001$) (Table 2). After correction for multiple comparisons (Bonferroni), the 2-loci combinatorial analysis showed that, in the presence of Pro/Pro genotype, the −1279G/A variant did not show any association with type 2 diabetes mellitus ($P = .24$); however, in the presence of 12Ala allele, the −1279 G/A variant showed a significant protective effect against type 2 diabetes mellitus ($P = .0003$) adjusted for age, sex, and BMI.

3.5. Haplotype analysis

Table 3 shows the D' values for the 3 variants, −1279G/A, Pro12Ala, and His478His, in the *PPARG2* gene in cases and controls. The haplotype *A-Ala-T* (−1279G/A-Pro12Ala-His478His) was significantly at a higher frequency among the NGT subjects compared with the diabetic subjects ($P < .0001$). The P value remained statistically significant even after Bonferroni correction ($P = .0002$). Linear regression analysis was carried out for analyzing the association of *PPARG2* haplotypes with the different quantitative traits such as BMI, waist circumference, fasting blood glucose, fasting insulin, and other biochemical characteristics. However, there was no association between the haplotypes of *PPARG2* and quantitative traits.

Table 2
Two-loci analysis involving the genotypes of the variants Pro12Ala and –1279G/A of *PPARG2* gene with type 2 diabetes mellitus

−1279G/A	NGT subjects	Type 2 diabetes mellitus subjects	Total	*P* value
Pro/Pro subjects				
GG	867 (96.6%)	688 (93.8%)		
XA (GA + AA)	30 (3.4%)	45 (6.2%)		
	897	733	1630	.018
Unadjusted OR				
GG vs XA	1.891 (95% CI, 1.14-3.14)			.014
OR adjusted for age, sex, and BMI				
GG vs XA	2.092 (95% CI, 1.22-3.59)			.008
X/Ala subjects				
GG	39 (19.3%)	79 (47.0%)		
XA (GA + AA)	163 (80.7%)	89 (53.0%)		
	202	168	370	.000002
Unadjusted OR				
GG vs XA	0.268 (95% CI, 0.16-0.46)			<.0001
OR adjusted for age, sex, and BMI				
GG vs XA	0.270 (95% CI, 0.15-0.49)			<.0001

Table 3
Haplotype analysis involving −1279G/A, Pro12Ala, and His478His variants at the *PPARG2* gene locus

Pairwise LD values (D') estimated using Arlequin* version 3.0 among the 3 loci		
	NGT subjects	Type 2 diabetes mellitus subjects
−1279G/A-Pro12Ala	0.5864	0.5645
Pro12Ala-His478His	0.5753	0.4361
1279G/A-His478His	0.7935	0.5468

Haplotype frequencies in cases and controls			
Haplotypes (1279G/A-Pro12Ala-His478His [C/T])	NGT subjects	Type 2 diabetes mellitus subjects	*P* value
G-Pro-C	0.8496	0.8490	
A-Ala-T	0.0440	0.0276	$P < .0001$

LD indicates linkage disequilibrium.
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4. Discussion

The important finding of this study is that the 3 variants of the *PPARG2* gene are not independently associated with type 2 diabetes mellitus; but as 2 loci (Pro12Ala and −1279G/A) and as a haplotype (*A-Ala-T*), they show a protective effect against the development of diabetes. This is one of the first reports investigating the association of these 3 variants with type 2 diabetes mellitus in Asian Indians.

The frequency of the A allele of the −1279G/A variant in the NGT and type 2 diabetes mellitus subjects was not statistically significant (0.08 vs 0.07, $P = .321$). This is the first study of the −1279G/A variant reporting on the genotype and allele frequencies; and hence, no genotype and allele frequency data from other populations are available for comparison. None of the clinical and biochemical parameters were statistically significant between the genotypes with and without the A allele of −1279G/A variant among the NGT and type 2 diabetes mellitus subjects.

The genotype and the allele frequencies of the Pro12Ala variant were not statistically significant between NGT and type 2 diabetes mellitus subjects. The results of this study are

in contrast to that of Altshuler and coworkers [23], which showed a decreased risk of type 2 diabetes mellitus in association with this variant. However, they used a family-based design to control for population stratification, whereas this study used a case-control association study. We failed to observe differences in body fat distribution, plasma insulin levels, and insulin sensitivity index by HOMA model between NGT subjects with and without the variant. This is contrary to the previous report that the Ala allele was associated with improved insulin sensitivity [24]. However, our findings were consistent with our earlier report where we showed that Pro12Ala is not associated with type 2 diabetes mellitus and insulin sensitivity in South Asians [18].

The genotype and the allele frequencies of the His478His variant were also not statistically significant between NGT and type 2 diabetes mellitus subjects. This finding is in accordance with the earlier reports from different ethnic origins [25-27].

Two-loci analysis revealed that the −1279G/A variant exhibits an increased susceptibility to type 2 diabetes mellitus (OR, 2.092; $P = .008$) in the presence of Pro/Pro genotype and a protective effect against type 2 diabetes mellitus (OR, 0.270; $P < .0001$) in the presence of 12Ala allele. Hence, the presence of heterozygous condition of both the variants makes an individual protective against development of type 2 diabetes mellitus. This finding explains the fact why some individuals having the Pro12Ala variant are protected from type 2 diabetes mellitus, whereas others are not. This is the first study demonstrating the association of the promoter −1279G/A variant in combination with the Pro12Ala of *PPARG2* gene with type 2 diabetes mellitus and hence is of great significance. Further studies are needed to investigate the biochemical basis of this association and its possible relation to type 2 diabetes mellitus.

The *A-Ala-T* haplotype showed an association with the reduced risk of type 2 diabetes mellitus. This is consistent with the other studies that have shown an association of the haplotypes of *PPARG2* gene with type 2 diabetes mellitus and its related traits [28,29].

Other variants such as Pro115Gln mutation, which blocks the phosphorylation of *PPARG2* at Ser 114 [30], and Val290Met and Pro467Leu mutations [31], the first germline loss-of-function mutations identified in *PPARG2* gene and found in the ligand binding domain of *PPARG2*, were not identified in the pilot screening in this study population.

In conclusion, our findings suggest that the Pro12Ala variant does not show a protective effect independently but in combination with the −1279G/A promoter variant exhibits a protective effect against the development of type 2 diabetes mellitus in South Indians. We also show that the *A-Ala-T* haplotype at the *PPARG2* locus is associated with the reduced risk of type 2 diabetes mellitus. Because the observed associations in the present study are at a statistical (rather than biological) level, independent study will be needed to confirm and further characterize these associations at a biological level.

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