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Original Article

Association Study of *IRS1* Gene Polymorphisms with Type 2 Diabetes in South Indians

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Abstract

Background and Objectives: The *insulin receptor substrate-1* (*IRS1*) gene is a candidate gene for type 2 diabetes. The aim of this study was to investigate the association of the *IRS1* gene polymorphisms Gly972Arg and Ala513Pro with type 2 diabetes in an Asian Indian population in south India.

Methods: A total of 2,148 subjects (1,187 normal glucose-tolerant [NGT] and 961 type 2 diabetes subjects) were randomly selected from the Chennai Urban Rural Epidemiology Study. The *IRS1* gene polymorphisms Gly972Arg and Ala513Pro were genotyped in these subjects using polymerase chain reaction–restriction fragment length polymorphism, and a few variants were confirmed by direct sequencing.

Results: The frequency of the "A" allele of the Gly972Arg(G→A) single nucleotide polymorphism was similar between the NGT and diabetes subjects (2%). There was no significant difference in the genotypic frequency between the NGT and type 2 diabetes group ($P = 0.25$). When the study subjects were stratified based on body mass index (BMI) as per World Health Organization Asia Pacific guidelines as nonobese (BMI $<25\,kg/m^2$) and obese (BMI $\geq 25\,kg/m^2$), neither the allelic frequency (nonobese, $P = 0.44$; obese, $P = 0.37$) nor the genotypic frequency (nonobese, $P = 0.29$; obese, $P = 0.35$) was significantly different between the NGT and type 2 diabetes groups. The Ala513Pro polymorphism was first genotyped in 500 NGT and 500 type 2 diabetes subjects. None of these subjects carried the Ala513Pro or the Pro513Pro genotype. Hence, the Ala513Pro polymorphism was not genotyped further.

Conclusion: The *IRS1* gene variants Gly972Arg and Ala513Pro are not associated with type 2 diabetes in this south Indian population.

Introduction

Insulin receptor substrate-1 (IRS1) is the principal substrate for the insulin receptor. It is thought to act as a multisite docking protein that binds signal proteins and links the insulin receptor kinase to a variety of cellular functions that are regulated by insulin.[1,2] For this reason, the *IRS1* gene is a candidate for type 2 diabetes. Two single nucleotide polymorphisms, namely, Gly972Arg and Ala513Pro, in the *IRS1* gene have been reported to be associated with type 2 diabetes in whites.[3] The Gly972 residue is located between two potential sites of tyrosine phosphorylation, and the Ala513Pro variant is located near the known binding site for the p85 regulatory subunit of the phosphoinositide 3-kinase.[2]

The *IRS1* Gly972Arg polymorphism is among the most extensively studied genetic variants in relation to type 2 diabetes. Although some studies have indicated a higher prevalence of Arg972 polymorphism in type 2 diabetes patients,[3–5] some studies have reported a weak[6] or no[7,8] association between this variant and type 2 diabetes. A study on South Indian and Finnish subjects failed to show an association of the Arg972 variant with type 2 diabetes;[9] however, a combined analysis of these two ethnic groups along with subjects from Danish and French ethnic groups showed an increased prevalence of the Arg972 polymorphism in subjects with type 2 diabetes.

Several explanations for this diversity in findings have been suggested. The effect of the *IRS1* variant may differ because of small sample size or ethnicity[10] or by degree of obesity.[11] In addition, significant regional differences in the prevalence of the Arg972 polymorphism has also been observed,[12] thus complicating the interpretation of association studies of this *IRS1* variant. In this respect, replication studies within the

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same ethnic group are a more robust choice, especially in populations such as Asian Indians, who have greater insulin resistance, increased susceptibility to type 2 diabetes, and a strong genetic background.[13] Hence, the present study was designed to investigate the association of Gly972Arg (rs1801278) and Ala513Pro (rs1801276) polymorphisms of the *IRS1* gene with type 2 diabetes in an Asian Indian population from south India.

Research Design and Methods

Subjects

A total of 2,148 unrelated subjects were chosen from the Chennai Urban Rural Epidemiology Study (CURES). The methodology of the study has been published elsewhere.[14] In Phase 1 of CURES, 26,001 subjects were recruited based on a systematic random sampling technique. Self-reported diabetes subjects were classified as "known diabetes subjects." In Phase 2 of CURES, all known diabetes subjects ($n = 1,529$) were invited to our center for detailed studies, of whom 1,382 responded. In Phase 3 of CURES, every 10th individual from Phase 1 ($n = 2,600$) was invited to undergo an oral glucose tolerance test using a 75-g oral glucose load (dissolved in 250 mL of water). Those who had a 2-h plasma glucose value $\geq$11.1 mmol/L (200 mg/dL) (based on World Health Organization Consulting Group criteria) were labeled as "newly detected diabetes subjects" ($n = 222$). Subjects who had a fasting plasma glucose value of $<$5.6 mmol/L (100 mg/dL) and 2-h plasma glucose value of $\leq$7.8 mmol/L (140 mg/dL) were categorized as normal glucose-tolerant (NGT)[15] ($n = 1,736$). The total number of diabetes subjects in the CURES study population is 1,604 (1,382 known diabetes subjects plus 222 newly detected diabetes subjects). From these 1,604 diabetes subjects 961 subjects and from the 1,736 NGT subjects 1,187 subjects were randomly selected for the present study. Informed consent was obtained from all the subjects who participated in this study, and the study was approved by the institutional ethical committee.

Biochemical measurements

Anthropometric measurements including weight, height, and waist were obtained using standardized techniques. The body mass index (BMI) was calculated as the weight (in kg) divided by the square of height (in m). The subjects chosen for the study were categorized according to their BMI as per the Asia-Pacific guidelines[16] (nonobese, BMI $<25\,kg/m^2$; obese, BMI $\geq 25\,kg/m^2$). Biochemical analyses were carried out on a Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany) using commercial kits (Roche Diagnostics, Mannheim). Fasting plasma glucose was estimated using the glucose oxidase–peroxidase method. Serum cholesterol was estimated using the cholesterol oxidase–phenol 4-amino antipyrene peroxidase method. Serum triglyceride was estimated using the glycerol phosphatase oxidase–phenol 4-amino antipyrene peroxidase method. High-density lipoprotein cholesterol was estimated using the polyethylene glycol–pretreated enzyme method, and low-density lipoprotein cholesterol was calculated using the formula of Friedewald et al.[17] Glycated hemoglobin was estimated by high-performance liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA).

Genotyping

DNA was isolated from whole blood using the phenol–chloroform method. Genotyping of the two polymorphisms was done by polymerase chain reaction–restriction fragment length polymorphism as described elsewhere.[18] To assure that the genotyping was of sufficient quality, random duplication in about 20% of the samples was performed by a technician who was blinded to the phenotype. There was 99% concordance in the genotyping. Furthermore, a few variants were confirmed by direct sequencing with an ABI 310 genetic analyzer (Applied Biosystems, Foster City, CA).

Statistical analysis

SPSS Windows version 10.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. One-way analysis of variance was used to compare groups for continuous variables. Data for continuous variables were expressed as mean $\pm$ SD values. The χ^2 test was used to compare the proportions of genotypes or alleles. P values of <0.05 were considered statistically significant.

Results

Gly972Arg polymorphism

Subject characteristics. The Gly972Arg polymorphism was genotyped in 1,187 NGT subjects and 961 type 2 diabetes subjects. The diabetes subjects were older compared with the NGT subjects (49 ± 10 and 46 ± 11 years, respectively) (Table 1). A comparison between diabetes and NGT subjects showed that the age- and sex-adjusted BMI, waist circumference, fasting plasma glucose, glycated hemoglobin, fasting serum insulin, total cholesterol, serum triglycerides, and low-density lipoprotein cholesterol were all significantly higher in the type 2 diabetes subjects ($P < 0.001$).

Genotype and allele frequency. Table 2 shows the genotype and allele frequencies of the Gly972Arg (G→A) variant in the study subjects. The genotypic distribution in both the NGT and the type 2 diabetes group was in Hardy–Weinberg equilibrium. The frequency of the "A" allele was similar between the NGT and diabetes subjects. The frequency of the minor homozygous genotype AA was found to be very low in NGT (0.2%) and type 2 diabetes (0.1%) subjects. Hence, the GA and AA genotypes were combined together for all analyses. Compared with the GG genotype, the frequency of the GA + AA genotype was not significantly different between the NGT and type 2 diabetes groups ($P = 0.25$).

A meta-analysis of 27 studies inferred that the Gly972Arg variant may specifically increase the risk for type 2 diabetes that is symptomatic or characterized at a young age of onset.[19] In order to avoid this confounder, in this study, the type 2 diabetes subjects were initially classified as "known diabetes subjects" and "newly detected diabetes subjects," and the frequency of this variant in these two groups was compared with that in the NGT subjects (Table 2). The lack of association with diabetes in our study ($P = 0.054$) does not support the hypothesis that the Gly972Arg variant increases the risk for type 2 diabetes. The diabetes subjects were then classified as early-onset (age at onset of diabetes, 26–40 years) and late-onset (age at onset of diabetes, >40 years), and when these two groups were compared with the NGT group, no signifi-

Table 1. Clinical and Biochemical Characteristics of the Study Subjects

	NGT subjects	*Type 2 diabetes subjects*	P *value**
n (male/female)	1,187 (450/737)	961 (411/550)	—
Age (years)	46 ± 11	49 ± 10	—
BMI (kg/m^2)	23.7 ± 4.6	25.1 ± 4.3	<0.001
Waist circumference (cm)	84.4 ± 11.9	90.4 ± 10.0	<0.001
Fasting plasma glucose (mmol/L)	4.66 ± 0.5	9.27 ± 4.0	<0.001
2-h post-load plasma glucose (mg/dL)	5.66 ± 1.1	—	—
Fasting serum insulin (μIU/mL)	8.7 ± 6.2	—	—
Glycated hemoglobin (%)	5.6 ± 0.5	8.6 ± 2.1	<0.001
Total cholesterol (mmol/L)	4.75 ± 0.98	5.14 ± 1.04	<0.001
HDL cholesterol (mmol/L)	1.14 ± 0.26	1.09 ± 0.23	<0.001
LDL cholesterol (mmol/L)	2.99 ± 0.78	3.32 ± 1.01	0.001
Log transformed serum triglycerides (mmol/L)	1.18 ± 0.01	1.72 ± 0.01	<0.001

Data are mean ± SD values. Two-hour post-load plasma glucose and fasting serum insulin were not measured for the type 2 diabetes subjects.
*P value adjusted for age and sex.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGT, normal glucose-tolerant.

cant difference was observed in the allelic frequency ($P = 0.30$ and 0.26, respectively) or genotypic frequency ($P = 0.26$ and 0.28, respectively).

Previous reports have shown that the Gly972Arg polymorphism might predispose individuals to type 2 diabetes in the presence of excess body weight or obesity.[4,11,20] In order to test this hypothesis, the study subjects were stratified based on BMI as nonobese (BMI <25 kg/m^2) and obese (BMI ≥25 kg/m^2) (Table 3), and the association of the Gly972Arg variant with diabetes was analyzed. Neither the allelic frequency (nonobese, $P = 0.44$; obese, $P = 0.37$) nor the genotypic frequency (nonobese, $P = 0.29$; obese, $P = 0.35$) was significantly different between the NGT and type 2 diabetes groups, ruling out any gene environment interaction in this study population.

Association of the Gly972Arg single nucleotide polymorphism with clinical and biochemical parameters. Table 4 compares the clinical and biochemical characteristics of the study subjects classified as NGT and type 2 diabetes in relation to the GG and GA + AA genotypes. Although previous studies have shown an association of the Gly972Arg variant with fasting insulin levels,[3] none of the parameters including the serum insulin levels showed any association with the GA + AA genotype in the present study.

Ala513Pro polymorphism

The Ala513Pro polymorphism was genotyped in 500 NGT and 500 type 2 diabetes subjects. None of these subjects carried the Ala513Pro or the Pro513Pro genotype. Because the Pro allele was not found in the pilot study population, the Ala513Pro polymorphism was not genotyped further in larger numbers.

Discussion

The prevalence of the Gly972Arg polymorphism in this study contrasts with that found in whites[3] (4.3% vs. 10.6% in type 2 diabetes and 3.2% vs. 6.5% in control subjects, respectively), but the prevalence is comparable to that found in the Japanese population[6] (3.7% and 3.9%, respectively).

Table 2. Frequency of the Gly972Arg *Insulin Receptor Substrate-1* Variant in the Study Subjects

			Type 2 diabetes subjects (n = *961*)			
			History of diabetes		*Diabetes onset*	
	NGT subjects (n = *1,187*)	*Type 2 diabetes subjects* (n = *961*)	*Known* (n = *754*)	*Newly detected* (n = *207*)	*Early* (n = *279*)	*Late* (n = *682*)
Genotype						
GG	1148 (96.6%)	919 (95.6%)	716 (95.0%)	203 (98.1%)	266 (95.3%)	653 (95.8%)
GA	38 (3.2%)	41 (4.3%)	37 (4.9%)	4 (1.9%)	13 (4.7%)	28 (4.1%)
AA	1 (0.2%)	1 (0.1%)	1 (0.1%)	—	—	1 (0.1%)
P vs. NGT*		0.25	0.054	0.29	0.26	0.28
Allele frequency						
"G" allele	2,332 (98%)	1,879 (98%)	1,469 (97%)	410 (99%)	545 (97%)	1,334 (98%)
"A" allele	40 (2%)	43 (2%)	39 (3%)	4 (1%)	13 (3%)	30 (2%)
P vs. NGT		0.23	0.053	0.27	0.30	0.26

*χ^2 P value for GG versus GA + AA. GA and AA genotypes were combined as the frequency of the AA genotype was very low.
NGT, normal glucose-tolerant.

Table 3. Frequency of the Gly972Arg *Insulin Receptor Substrate-1* Variant in the Study Subjects Stratified According to Body Mass Index

	NGT subjects	*Type 2 diabetes subjects*	P *value (GG vs. GA + AA)*
Nonobese (BMI <25 kg/m^2)			
n	768	512	
Frequency of genotype			
GG	741 (96.5%)	488 (95.3%)	0.29
GA	26 (3.4%)	24 (4.7%)	
AA	1 (0.1%)	—	
Frequency of allele			
"G"	1,508 (98.1%)	1,000 (97.6%)	0.44
"A"	28 (1.9%)	24 (2.4%)	
Obese (BMI ≥25 kg/m^2)			
n	419	449	
Frequency of genotype			
GG	407 (97.1%)	431 (96.0%)	0.35
GA	12 (2.9%)	17 (3.8%)	
AA	—	1 (0.2%)	
Frequency of allele			
"G"	826 (98.5%)	879 (97.8%)	0.37
"A"	12 (1.5%)	19 (2.2%)	

BMI, body mass index; NGT, normal glucose-tolerant.

The finding of the present study that *IRS1* Gly972Arg was not associated with type 2 diabetes agrees with several earlier studies.[7,12,21,22] The positive associations that have been reported for type 2 diabetes[3] in other studies may represent a chance finding, particularly because a large number of studies of the *IRS1* Gly972Arg variant have been conducted on small sample sizes, and the meta-analysis of 27 previously published studies showed only mildly statistically significant differences ($P = 0.03$).[19]

Despite a growing body of literature suggesting that Gly972Arg may alter *IRS1* function in vitro and in vivo,[23–25] this variant, while affecting the attributes of glucose homeostasis such as fasting glucose and insulin, still does not appear to influence the overall type 2 diabetes risk. Another possibility is that the association signal reported by others may not be due to Gly972Arg itself, but due to another nearby genetic variant; elucidation of this possibility requires a thorough understanding of the haplotype structure of the *IRS1* region and a systematic assessment of its common genetic variation in very large diabetes patient samples.

Nevertheless, the proposed model from various functional studies[23,26] has been that Gly972Arg itself is the functional polymorphism and not a proxy for some other undiscovered variant. This is expected because the Gly972 residue is located between two potential sites of tyrosine phosphorylation involved in the binding of phosphoinositide 3-kinase. Replacement of the small uncharged amino acid, glycine, by the large positively charged arginine is likely to result in an impairment in the binding of the phosphoinositide 3-kinase with IRS1.[27]

The key finding of the present study is that despite a sample size ($n = 2{,}148$) larger than that of the previously reported study[9] in the same population ($n = 239$), no evidence of association was seen between the Gly972Arg *IRS1* variant and

Table 4. Clinical and Biochemical Characteristics of the Study Subjects According to Gly972Arg *Insulin Receptor Substrate-1* Genotypes

		Type 2 diabetes subjects		
	NGT subjects, GG (n = 1,148)	*GA + AA (n = 39)*	*GG (n = 919)*	*GA + AA (n = 42)*
BMI (kg/m^2)	23.6 ± 4.7	23.3 ± 4.2	25.2 ± 4.3	24.5 ± 4.4
Waist circumference (cm)	84.3 ± 11.9	83.2 ± 10.9	90.7 ± 10.0	90.3 ± 11.8
Fasting plasma glucose (mmol/L)	4.67 ± 0.4	4.62 ± 0.4	8.91 ± 3.9	8.96 ± 3.6
2-h post load plasma glucose (mmol/L)	5.55 ± 1.1	5.50 ± 1.1	—	—
Fasting serum insulin (μIU/mL)	8.8 ± 6.0	7.1 ± 5.0	—	—
Glycated hemoglobin (%)	5.7 ± 0.5	5.6 ± 0.7	8.7 ± 2.1	9.0 ± 2.3
Total cholesterol (mmol/L)	4.75 ± 0.96	4.55 ± 0.88	5.22 ± 1.06	5.33 ± 1.11
HDL cholesterol (mmol/L)	1.14 ± 0.26	1.22 ± 0.26	1.11 ± 0.23	1.17 ± 0.20
LDL cholesterol (mmol/L)	2.96 ± 0.80	2.80 ± 0.78	3.19 ± 0.96	3.25 ± 1.01
Log transformed serum triglycerides (mmol/L)	1.14 ± 0.01	1.10 ± 0.02	1.66 ± 0.01	1.71 ± 0.02

Data are mean ± SD values. None of the parameters showed any significant difference among the genotypes.

type 2 diabetes, and results did not differ even in the presence of obesity. Moreover, the findings of the present study are in agreement with the largest study on Gly972Arg consisting of 9,000 white individuals,[7] which also failed to observe an association of G972R with type 2 diabetes, related traits, and age of onset.

The absence of the Ala513Pro polymorphism in this study population is not surprising because this has been the case in Japanese,[28] Pima Indian,[29] South Indian,[9] Taiwanese,[18] or Turkish[22] subjects. However, this polymorphism has been repeatedly identified in white subjects, both in type 2 diabetes subjects and in controls.[3,11,12] This polymorphism was first detected in a Danish population,[3] and the frequency of this variant was found to be higher in individuals with diabetes (7%) than in the control subjects (2%). A large study on 971 UK type 2 diabetes subjects with strong family history and early-onset type 2 diabetes and 1,257 control subjects did not show any association of the Ala513Pro variant with type 2 diabetes.[21]

Although the absence of the Ala513Pro variant in the south Indian population has been reported already,[9] this study was undertaken as this variant is located near the Tyr-Met-X-Met (YMXM) motif around Tyr612, which is a known binding site for the p85 regulatory subunit of the phosphoinositide 3-kinase. However, functional studies have shown that the mutant was indistinguishable from wild-type *IRS1* in its ability to undergo tyrosine phosphorylation in response to insulin, to interact with SH2 domain–containing proteins, and to mediate insulin-stimulated increases in phosphoinositide 3-kinase activity.[2]

In conclusion, the present study indicates that the *IRS1* Gly972Arg and Ala513Pro variants are not associated with type 2 diabetes in south Indians.

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Author Disclosure Statement

No competing financial interests exist.

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