A Gly482Ser Polymorphism of the Peroxisome Proliferator-Activated Receptor-γ Coactivator-1 (PGC-1) Gene Is Associated with Type 2 Diabetes in Caucasians

( Gly482Ser polymorphism / PGC-1 / type 2 diabetes / association study )

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Abstract. The PGC-1 gene has been implicated in the regulation of several genes controlling energy metabolism. The prevalent Gly482Ser polymorphism of the PGC-1 gene has been shown to be associated with type 2 diabetes in some but not all studies. The aim of this study was to analyse whether the Gly482Ser variant is a risk factor for development of type 2 diabetes in Slovene population (Caucasians). Genotyping of the Gly482Ser polymorphism was performed for 545 subjects: 305 patients with type 2 diabetes and 240 non-diabetic controls. The Gly482Ser genotype distribution in patients with type 2 diabetes (AA = 11.5 %, AG = 42.3 %, GG = 46.2 %) differed from genotype distribution in non-diabetic controls (AA = 6.3 %, AG = 46.3 %, GG = 47.5 %), and the AA genotype was associated with 1.9-times increased risk of type 2 diabetes (95 % confidence interval 1.0–3.6; P = 0.036). In conclusion, we suggest that the AA genotype of the Gly482Ser polymorphism of the PGC-1 gene should be considered as a risk factor for the development of type 2 diabetes in Caucasians.

The peroxisome proliferator-activated receptor-γ coactivator-1 (PGC-1) gene was shown to be involved in the regulation of many aspects of energy metabolism, including adaptive thermogenesis, mitochondrial biogenesis, fatty acid β-oxidation, hepatic gluconeogenesis and glucose uptake (Barroso et al., 2003). Additionally, the PGC-1 gene was mapped to a chromosomal region 4p15.1 that was linked to fasting serum insulin concentrations (Pratley et al., 1998). The results of the association studies of the Gly482Ser polymorphism of the PGC-1 gene in type 2 diabetes are opposing, showing (1) an association with increased type 2 diabetes risk (Ek et al., 2001), (2) no association (Lacquemant et al., 2002; Hara et al., 2002; Muller et al., 2003) or (3) association with lower risk of type 2 diabetes (Barroso et al., 2003). Additionally, the polymorphism has been associated with insulin resistance (Hara et al., 2002), obesity indices in women (Esterbauer et al., 2002), and with lipid metabolism and insulin secretion (Muller et al., 2003).

In this association study we tested the hypothesis whether the Gly482Ser polymorphism in the PGC-1 gene is a risk factor for development of type 2 diabetes in Slovene population (Caucasians).

Material and Methods

The study population of this cross-sectional analysis consisted of 545 unrelated Slovene subjects: 305 type 2 diabetic and 240 non-diabetic. The Gly482Ser PGC-1 polymorphism was genotyped by polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) using primers: Gly482Ser-F: 5′-TAAA-GATGTCTCCTCTGATT-3′ and Gly482Ser-R: 5′-GGAGACACATTGAACAAATGAGGATTG-3′ followed by HpaII restriction. PCR amplification was carried out in a volume of 25 µl containing 200 ng genomic DNA, 0.1 mmol/l dNTP, 1 x PCR buffer, 1.5 mmol/l MgCl2, 0.5 µmol/l of each primer, and 0.5 units of Taq DNA-polymerase. The cycling programme was a denaturation step at 95°C for 8 min followed by 40 cycles of 94°C for 30 s, annealing at 50°C for 30 s, and elongation at 72°C for 2 min, followed by HpaII restriction (5 units) for 8 h. The restriction products were separated on 3% agarose gels. Chi-square test was used to compare discrete variables. Statistical analysis was performed using the SPSS program for Windows version 11 (SPSS Inc. Illinois).

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Abbreviation: PGC-1 – peroxisome proliferator-activated receptor-γ coactivator-1.

Table 1. Genotype and allele distribution of the PGC-1 Gly482Ser polymorphism in type 2 diabetic patients and in controls

<table>
<thead>
<tr>
<th>Genotype/allele</th>
<th>Type 2 diabetes, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95 % CI)1</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype: AA</td>
<td>35 (11.5)</td>
<td>15 (6.25)</td>
<td>1.9 (1.0-3.6)2</td>
<td>0.0362</td>
</tr>
<tr>
<td>AG</td>
<td>129 (42.3)</td>
<td>111 (46.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>141 (46.2)</td>
<td>114 (47.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>305</td>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allele: A</td>
<td>199</td>
<td>141</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>411</td>
<td>339</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1OR (95 % confidence interval), 2P-value and OR for recessive model (AA versus AG plus GG)

Results and Discussion

The Gly482Ser genotype distribution in patients and controls was compatible with Hardy-Weinberg expectations (Table 1; patients P = 0.51, χ² = 0.44; controls P = 0.075, χ² = 3.15). There were no statistically significant differences in age (59.9 ± 10.4 years vs. 58.9 ± 11.5 years), body mass index (27.7 ± 4.3 kg/m² vs. 27.5 ± 2.3 kg/m²) and incidence of male sex (45.5% vs. 42.1%) between patients and controls. There was a higher incidence of arterial hypertension (67.5 vs. 37.5, P < 0.001) and a lower incidence of smoking (15.4 vs. 50, P < 0.001) in patients than in controls. In a cross-sectional study, association between the AA genotype of the PGC-1 Gly482Ser polymorphism and type 2 diabetes in Slovene population was found (odds ratio (OR) 1.9, 95% confidence interval (CI) 1.0-3.6, P = 0.036). Our finding is in accordance with the results of the meta-analysis of the Gly482Ser polymorphism of the PGC-1 gene in Caucasian population (Parikh and Groop, 2004), where data from only three studies published until 2002 were reported (Ek et al., 2001; Andersen et al., 2002; Lacquemant et al., 2002). The genotype distribution of the Gly482Ser polymorphism in the diabetic and the control group in our study was similar to two studies published in meta-analysis (Ek et al., 2001; Andersen et al., 2002), whereas Lacquemant and co-workers (2002) failed to demonstrate an association. In contrast to our study, reports in Japanese population (Hara et al., 2002), in Pima Indians (Muller et al., 2003) and in Caucasians in Great Britain (Barroso et al., 2003) failed to demonstrate a positive association between the PGC-1 Gly482Ser polymorphism and type 2 diabetes. Different populations represent different gene pools, suggesting that gene-disease associations can be expected to vary between populations due to the differences in the complex genetic background.

Hara et al. (2002) demonstrated the PGC-1 Gly482Ser polymorphism to affect the fasting insulin level and insulin resistance index, and subjects with the AA genotype (Ser/Ser) were reported to have the highest fasting insulin level and insulin resistance index. We speculate that the effect of the PGC-1 Gly482Ser polymorphism on insulin secretion and resistance is important in the development of type 2 diabetes. However, even though the PGC-1 Gly482Ser polymorphism has been demonstrated to be associated with type 2 diabetes in Slovene population, it might not be the only causative polymorphism but could be in linkage disequilibrium with an as yet unidentified aetiological variant.

In conclusion, we suggest that the Gly482Ser polymorphism of the PGC-1 gene should be considered as a risk factor for type 2 diabetes in Slovene population (Caucasians).

References


