Associations of \textit{PPARGC1A} Haplotypes With Plaque Score but Not With Intima-Media Thickness of Carotid Arteries in Middle-Aged Subjects

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\textbf{Background and Purpose}—Peroxisome proliferator activated receptor \(\gamma\) coactivator 1\(\alpha\) (PGC-1\(\alpha\), \textit{PPARGC1A}) integrates the transcriptional program of mitochondrial biogenesis. Mitochondria are the main source of cellular reactive oxygen species implicated in atherogenesis. We therefore ascertained associations of \textit{PPARGC1A} polymorphisms with asymptomatic carotid atherosclerosis.

\textbf{Methods}—Eight single nucleotide polymorphisms tagging two haplotype blocks within \textit{PPARGC1A} were studied in 1379 participants of the Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk. Early atherosclerosis was assessed by intima-media thickness and extent of plaques (B-score) of the carotid arteries.

\textbf{Results}—No associations of carotid artery intima-media thickness measurements with block 1 or 2 haplotype distributions or individual haplotypes were observed. However, the block 1 haplotype carrying the variant C nucleotide at \(-3974\) relative to the transcription start site was associated with disease status defined by the presence of more than one minimal lesion and the \(-3974\) C allele was associated with decreased risk (odds ratio=0.60, \(P=0.007\)) after adjustment for linkage disequilibrium between single nucleotide polymorphisms.

\textbf{Conclusions}—These results are consistent with the concept that risk factors for distinct carotid phenotypes may vary and suggest, but do not prove, that PGC-1\(\alpha\) may contribute to the regulation of atherogenic pathways. (\textit{Stroke}. 2006;37:2260-2265.)

\textbf{Key Words}: carotid atherosclerosis \(\boldsymbol{\blacktriangledown}\) haplotype \(\boldsymbol{\blacktriangledown}\) peroxisome proliferator activated receptor gamma coactivator \(\boldsymbol{\blacktriangledown}\) reactive oxygen species

Atherosclerotic cardiovascular disease is a complex disorder that results from genetic and environmental factors. Among pathogenetic factors, an excessive burden of reactive oxygen species (ROS) in cells of the vascular wall is well established.\(^1\) Although ROS are generated in diverse cellular compartments, the majority of cellular ROS originates in mitochondria, where complex I and III have been implicated as the major sites of ROS production.\(^2\) Specific antioxidant enzymes within or outside the mitochondria defend against excessive amounts of cellular ROS. Peroxisome proliferator activated receptor \(\gamma\) coactivator 1\(\alpha\) (PGC-1\(\alpha\)) is a transcriptional coactivator that serves to integrate diverse transcriptional pathways, including mitochondrial biogenesis.\(^3,4\) PGC-1\(\alpha\) is expressed in human arterial wall cells.\(^5\) We previously identified several polymorphisms within \textit{PPARGC1A} encoding PGC-1\(\alpha\). These polymorphisms were located in two distinct haplotype blocks, each characterized by five common haplotypes.\(^6\) Because of the central role of PGC-1\(\alpha\) in mitochondrial biogenesis and function, we tested the hypothesis that the \textit{PPARGC1A} locus is associated with sonographic phenotypes of preclinical carotid atherosclerosis in a well-defined Austrian population.

\textbf{Materials and Methods}

\textbf{Study Population}
We studied 40- to 60-year-old male \((n=886)\) and 45- to 65-year-old female \((n=493)\) participants of the Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk (SAPHIR). Study purpose, recruitment procedures, and population characteristics have been detailed elsewhere.\(^7\) All study subjects provided informed consent, and the study was approved by the local ethics committee. Type 2 diabetes and hypertension was defined as described.\(^5,6\)

Intima-media thickness (IMT) and plaque extent of the near and far walls of the common and internal carotid arteries and the bifurcations were measured by high-resolution B-mode ultrasound (ATL HDI 3000; Philips Medical Systems) according to the ACAPS protocol\(^8\) as described.\(^9\) Average IMTs represent the means from all individual measurements and maximum IMTs represent the highest single

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measurement at any site. Complete IMT measurements were available in 835 men and 486 women. B-scores were obtained by grading on a 5-point scale ranging from 0 (normal) to 5 (complete luminal obstruction). Adding the B-score of all segments resulted in a sum B-score. For case definition, ie, individuals with preclinical carotid atherosclerosis, a sum B-score >1 was used. Subjects with incomplete genotyping results were excluded. To reduce possible confounding resulting from therapeutic strategies, subjects with symptomatic atherosclerotic diseases (myocardial infarction, angina pectoris, stroke, transitory ischemic attack, peripheral arterial disease) were excluded.

**Laboratory Determinations**

**PPARGC1A** single-nucleotide polymorphisms (SNPs) in haplotype block 1 at gene positions −3974 T/C (rs2970865), −3833 A/C (rs1878949), −3629 T/G (rs4383605), and −1437 T/C (rs 2970870) and in block 2 at +75657 C/T (rs2970847), +75919 G/A (rs8192678), +76059 A/G (rs3755863), and +94581 C/T (rs6821591) were determined. Positions are relative to the translation start site in the genomic sequence. SNPs 75657, 75919, 76059, and 94581 in the coding region correspond to positions 1302, 1564, 1564, and 2962, respectively, in the mRNA sequence relative to the translational start site. Among variant sites, only the +1564 SNP results in a 3629 T/G (rs4383605), and 75657 C/T (rs2970847), and +76059 A/G (rs3755863), and +94581 C/T (rs6821591) were determined. Positions are relative to the translation start site in the genomic sequence. SNPs 75657, 75919, 76059, and 94581 in the coding region correspond to positions 1302, 1564, 1564, and 2962, respectively, in the mRNA sequence relative to the translational start site. Among variant sites, only the +1564 SNP results in an amino acid change (Gly/Ser). SNP qualifiers refer to database entries (www.ncbi.nlm.gov/SNP/). Other laboratory parameters were determined as described.

**Statistics**

Differences of continuous variables between cases and controls were ascertained by 2-way analysis of variance. Logarithmic transformations were made if the equal variance and normality assumptions of analysis of variance of random effects were violated. Allele frequencies were estimated by gene counting. Agreement with Hardy-Weinberg expectations was tested using achi-square goodness-of-fit test. Differences in genotype frequencies between cases and controls were determined using a chi-square distribution with 2 degrees of freedom. Odds ratios (ORs) with confidence intervals (95% CIs) for each genotype with the respective wild type as the reference were determined as described. Standardized pairwise linkage disequilibrium (LD) expressed in terms of D′ and r2 parameters and haplotype frequencies were estimated using the THESIAS software (www.genecanvas.org). The THESIAS program was also used for testing association between haplotypes and phenotypes of interest. This program is based on a maximum likelihood approach and allows the simultaneous estimation of haplotype frequencies and haplotype–phenotype association parameters possibly adjusted for covariates. Covariate-adjusted haplotype–phenotype parameters, expressed as OR for binary phenotypes or mean effect for continuous phenotypes, were estimated for each haplotype by comparison to the most frequent haplotype. Results provided by the THESIAS software were then compared for consistency to those obtained using the haplo.score software (http://www.mayo.edu/statgen/).

**Results**

Age and body mass index as well as the prevalence of hypertension were higher in cases than in controls. Cholesterol, apolipoprotein B, and C-reactive protein levels were higher in subjects with asymptomatic disease, whereas the inverse relationship was observed for high-density lipoprotein cholesterol (Table 1). Men were more often smokers than women. Women displayed lower levels of glucose and triglycerides but higher levels for high-density lipoprotein cholesterol, apoA-I, and C-reactive protein. No heterogeneity across sex was observed in case–control association analyses.

The locations of the eight SNPs, their reference numbers, and minor allele frequencies, determined in cases and con-

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**TABLE 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Trait</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=389)</td>
<td>Controls (n=497)</td>
</tr>
<tr>
<td>Age, years</td>
<td>51.3 (4.8)</td>
<td>47.4 (5.1)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.6 (3.9)</td>
<td>26.6 (3.5)</td>
</tr>
<tr>
<td>Smoking, y/n</td>
<td>86/303</td>
<td>115/382</td>
</tr>
<tr>
<td>Hypertension, y/n</td>
<td>188/201</td>
<td>149/348</td>
</tr>
<tr>
<td>Type 2 diabetes, y/n</td>
<td>20/369</td>
<td>17/480</td>
</tr>
<tr>
<td>Menopause, y/n</td>
<td>199/45</td>
<td>205/44</td>
</tr>
<tr>
<td>Hormone replacement therapy, y/n</td>
<td>63/136</td>
<td>88/117</td>
</tr>
</tbody>
</table>

Glucose, mmol/L‡               | 5.13 (0.48)   | 5.18 (0.49)     | 4.92 (0.74)   | 5.01 (0.56)     | 0.0253§ | 0.0001 |
Insulin, pmol/L‡               | 43.4 (22.0)   | 43.3 (23.0)     | 42.2 (24.5)   | 42.4 (22.4)     | NS | NS |
Cholesterol, mmol/L            | 6.10 (1.03)   | 5.74 (0.98)     | 6.05 (1.03)   | 5.89 (1.01)     | 0.0001 | NS |
Triglyceride, mmol/L           | 1.59 (1.19)   | 1.45 (1.04)     | 1.25 (0.63)   | 1.15 (0.55)     | 0.0144§ | 0.0001 |
High-density lipoprotein cholesterol, mmol/L | 1.42 (0.34)   | 1.47 (0.34)     | 1.68 (0.41)   | 1.76 (0.44)     | 0.0001 | 0.0001 |
Apolipoprotein AI, g/L         | 1.50 (0.23)   | 1.52 (0.22)     | 1.65 (0.29)   | 1.69 (0.27)     | 0.0160§ | 0.0001 |
Apolipoprotein B, g/L          | 1.21 (0.26)   | 1.12 (0.24)     | 1.15 (0.24)   | 1.10 (0.23)     | 0.0001 | 0.0165§ |
C-reactive protein, mg/L       | 2.68 (4.50)   | 1.93 (2.58)     | 4.05 (6.43)   | 3.33 (3.86)     | 0.0022 | 0.0001 |

Cases are defined by a sum B-score >1. Data are numbers of observations or untransformed means (SD). Body mass index is adjusted for age; other continuous variables are adjusted for age and body mass index. *Cases versus controls; †males versus females; ‡subjects with diabetes are excluded; §P values not significant after the Bonferroni correction. NS indicates not significant.
controls of the current study population, are shown in Figure. All polymorphisms fulfilled Hardy-Weinberg expectations. Allele and genotype distributions of each SNP tested did not differ between cases and controls consistently in males and females (supplemental Table I, available online at http://stroke.ahajournals.org).

As expected, the pairwise LD matrix revealed 2 main haplotype blocks (Table 2; Figure). The first one includes the polymorphisms in the promoter region (T-3974C, A-3833G, T-3629G, and T-1437C), whereas the second includes those located in the transcribed region (C/H1100175657C/T, G/H1100175919G/A, A/H1100176059A/G, C/H1100194581C/T). In each haplotype block, 5 common haplotypes with frequencies >0.01 were inferred that accounted for >98% of the chromosomes (Table 3). For each of the common haplotypes, the squared correlation between true and predicted haplotype dose was >0.97 (data not shown). In each block, the respective four SNPs were necessary to tag the five common haplotypes. Because of this LD pattern, haplotype analysis was performed in each block separately.

The test for a global association between block 1 haplotypes and plaque score was borderline ($\chi^2 = 8.656$, 4 degrees of freedom [df], $P = 0.071$). In particular, the CATT haplotype was less frequent in cases than in controls (0.178 versus 0.200), was associated with lower risk of disease (OR = 0.79, 95% CI = 0.62 to 0.99, \(P = 0.048\)) and consistently with the lowest haplotypic Z-score (Table 3). Because this haplotype was the only one carrying the TATT C allele, comparison of the TATT and CATT haplotypes differing by a single substitution provided a

### TABLE 2. Paired Linkage Disequilibrium Statistics of PPARGC1A Polymorphisms

<table>
<thead>
<tr>
<th>Position</th>
<th>Exchange</th>
<th>MAF cases</th>
<th>MAF controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>76059</td>
<td>75919</td>
<td>75657</td>
<td>-1437</td>
</tr>
<tr>
<td>94581</td>
<td>13</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are standardized pairwise linkage disequilibrium coefficients $D^*$ or $r^2$ (in parentheses).

* $P < 0.01$; † $P < 0.001$; ‡ not significant; § $P < 0.05$; all other $P < 0.0001$. 

Polymorphic sites and haplotype blocks in PPARGC1A. Linear map with exons (full boxes); SNP positions are relative to the translational start site; MAF indicates minor allele frequency; SNP qualifiers refer to database entries (www.ncbi.nlm.gov/SNP). Promoter SNPs not typed in this study, but being in complete linkage disequilibrium with typed SNPs, are shown above the linear map. The extension of haplotype blocks is shown at the bottom.
TABLE 3. **PPARGC1A** Block 1 and 2 Haplotypes and Asymptomatic Carotid Atherosclerosis

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Polymorphisms</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)*</th>
<th>P</th>
<th>Z-Score</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1111</td>
<td>−3974 T/C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1112</td>
<td>T A T T</td>
<td>0.073</td>
<td>0.056</td>
<td>1.31 (0.92 to 1.87)</td>
<td>0.128</td>
<td>1.731</td>
<td>0.084</td>
</tr>
<tr>
<td>1121</td>
<td>T A G T</td>
<td>0.256</td>
<td>0.265</td>
<td>0.96 (0.78 to 1.19)</td>
<td>0.722</td>
<td>0.168</td>
<td>0.867</td>
</tr>
<tr>
<td>1212</td>
<td>T G T C</td>
<td>0.309</td>
<td>0.314</td>
<td>1.00†</td>
<td>0.181</td>
<td>0.856</td>
<td></td>
</tr>
<tr>
<td>2111</td>
<td>C A T T</td>
<td>0.159</td>
<td>0.146</td>
<td>1.04 (0.81 to 1.34)</td>
<td>0.761</td>
<td>0.725</td>
<td>0.468</td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75657 C/T</td>
<td>75919 G/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1111</td>
<td>C G A C</td>
<td>0.307</td>
<td>0.328</td>
<td>0.91 (0.75 to 1.11)</td>
<td>0.365</td>
<td>−1.695</td>
<td>0.090</td>
</tr>
<tr>
<td>1112</td>
<td>C G A T</td>
<td>0.107</td>
<td>0.094</td>
<td>1.15 (0.86 to 1.53)</td>
<td>0.358</td>
<td>1.067</td>
<td>0.286</td>
</tr>
<tr>
<td>1122</td>
<td>C G G T</td>
<td>0.065</td>
<td>0.046</td>
<td>1.36 (0.94 to 1.97)</td>
<td>0.105</td>
<td>1.851</td>
<td>0.064</td>
</tr>
<tr>
<td>1222</td>
<td>C A G T</td>
<td>0.331</td>
<td>0.331</td>
<td>1.00†</td>
<td>0.055</td>
<td>0.956</td>
<td></td>
</tr>
<tr>
<td>2111</td>
<td>T G C A</td>
<td>0.178</td>
<td>0.200</td>
<td>0.79 (0.62 to 0.99)</td>
<td>0.048</td>
<td>−2.453</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Cases are defined by a sum B-score >1.

*OR relative to the most common haplotype; †Reference haplotype; analyses were adjusted for age, sex, body mass index, smoking status, cholesterol, high-density lipoprotein cholesterol, hypertension, and C-reactive protein. The likelihood ratio test statistics for global haplotypic effects were $\chi^2 = 8.656$, 4 df, $P = 0.071$ and $\chi^2 = 9.151$, 4 df, $P = 0.026$ for block 1 and 2 haplotype analyses, respectively.

Discussion

PGC-1α has recently attracted much attention because of its central importance in a number of metabolic programs, including hepatic gluconeogenesis, thermogenesis, and mito-

TABLE 4. **PPARGC1A** Block 1 Haplotypes and Preclinical Carotid Atherosclerosis

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Polymorphisms</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)*</th>
<th>P</th>
<th>Z-Score</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3974 T/C</td>
<td>−3833 A/G</td>
<td>0.086</td>
<td>0.057</td>
<td>1.43 (0.98−2.12)</td>
<td>0.0643</td>
<td>2.514</td>
<td>0.0119</td>
</tr>
<tr>
<td>1112</td>
<td>T A T C</td>
<td>0.238</td>
<td>0.267</td>
<td>0.84 (0.66−1.08)</td>
<td>0.1746</td>
<td>−0.869</td>
<td>0.3846</td>
</tr>
<tr>
<td>1121</td>
<td>T A G T</td>
<td>0.309</td>
<td>0.313</td>
<td>1.00†</td>
<td>0.436</td>
<td>0.6629</td>
<td></td>
</tr>
<tr>
<td>1212</td>
<td>T G T C</td>
<td>0.167</td>
<td>0.148</td>
<td>1.01 (0.75−1.37)</td>
<td>0.9182</td>
<td>0.686</td>
<td>0.4930</td>
</tr>
<tr>
<td>2111</td>
<td>C A T T</td>
<td>0.168</td>
<td>0.196</td>
<td>0.73 (0.55−0.97)</td>
<td>0.0293</td>
<td>−2.505</td>
<td>0.0122</td>
</tr>
</tbody>
</table>

Cases are defined by at least one score 2-lesion; 294 cases and 1085 controls.

*OR relative to the most common haplotype; †Reference haplotype; analyses were adjusted for age, sex, body mass index, smoking status, cholesterol, high-density lipoprotein cholesterol, hypertension, and C-reactive protein. The likelihood ratio test statistics for global haplotypic effects were $\chi^2 = 11.88$, 4 df, $P = 0.0136$. 

measurements were observed in the entire study population (supplemental Table III, available online at http://stroke.ahajournals.org), suggesting that block 1 haplotypes mainly influenced lesion development. To further test this notion, we reclassified the case–control status in that at least one score 2 lesion (1.5 to 2 mm) had to be detected in cases. Using this case definition, block 1 haplotype distributions differed between cases and controls ($\chi^2 = 11.88$, 4 df, $P = 0.0136$; Table 4). In addition, the risk reduction of the CATT haplotype was maintained ($\chi^2 = 0.73$, CI = 0.55 to 0.97, $P = 0.0293$; Table 4). Moreover, the −3974 C allele adjusted for LD between SNPs was associated with reduced risk (OR = 0.51, CI = 0.33 to 0.78, $P = 0.0017$). Furthermore, adjustment for average IMT of common carotid arteries along with established risk factors revealed a significant global haplotype effect ($P = 0.005$) and the lowest Z-score for the CATT haplotype ($P = 0.0264$) among block 1 haplotypes.

Discussion

PGC-1α has recently attracted much attention because of its central importance in a number of metabolic programs, including hepatic gluconeogenesis, thermogenesis, and mito-
chloridrial biogenesis and function.3,4,14 Although a possible role of PGC-1α in atherogenesis has not been addressed in animal models, studies in human, bovine, and mouse endothelial cells suggested that overexpression of PGC-1α reduces ROS accumulation and apoptotic cell death under basal and oxidative stress conditions.15 Our studies in humans suggesting an association of promoter haplotypes with preclinical carotid atherosclerosis is consistent with a role of PGC-1α in atherogenesis.

Ultrasonographic carotid measurements reveal distinct carotid phenotypes with increased IMT and plaques or focal thickening of the carotid wall. Although associations of both phenotypes with each other and various disease endpoints are well documented,15,16 the two phenotypes may have common and distinct determinants.17–19 According to previous reports, IMT is more strongly related to stroke than myocardial infarction, whereas plaques may be stronger predictors of myocardial infarction and early parental death from coronary heart disease.13,20 Our studies support the concept that increased IMT and plaque burden in carotid arteries is associated with common and distinct risk factors and/or may reflect different stages of the disease. The selective association with focal intima-media thickening was corroborated by case-control reclassification in that similar associations were observed when slightly more advanced plaques were used for discrimination. Moreover, these associations were maintained after adjustment for average IMT. Thus, our results suggest, but do not prove, an effect of PGC-1α on lesion development. Regulation of mitochondrial antioxidant defense in cells of the vascular wall would be consistent with a localized effect of PGC-1α. Indeed, ectopic expression of PGC-1α in human umbilical vein endothelial cells upregulated mitochondrial detoxification proteins such as manganese superoxide dismutase, periredoxins 3 and 5, mitochondrial thioredoxin, and mitochondrial thioredoxin reductase, and, to a lesser extent, uncoupling protein 2.15 Thus, several downstream targets of PGC-1α may contribute to the regulation of cellular ROS levels.

Among the promoter SNPs used for haplotype tagging, only the −3974 T/C SNP, when considered in its haplotype context, discriminated cases from controls. Because of the LD among the eight SNPs studied, a standard Bonferroni correction for multiple testing was not applied, because it would have been too conservative. Using the method proposed by Li and Ji,21 the number of independent components underlying the LD structure of the set of SNPs was estimated to be seven. After correcting for this number, which corresponds to considering significant any probability value of 0.007, the effect of the T-3947C SNP remained borderline but significant. This polymorphism is located in a putative transcription factor binding site and affects PGC-1α expression in INS1-E cells but has little effect in HepG2 or PA26 cells.6 Preliminary studies in THP-1 or human umbilical vein endothelial cells revealed minor effects of this SNP on the expression of a reporter gene under basal culture conditions (data not shown). However, phased genotyping in 46 alleles showed complete linkage disequilibrium among variable sites located at −3974, −3705, −1999, and −1789. The functionality of all these sites has not been tested, but the −1789 SNP is located in a MEF2C site that modulates the activity of another bona fide MEF2C site located at −1437.6,22 Thus, variant sites being in linkage disequilibrium with the −3974 SNP may influence PGC-1α expression in a tissue-specific manner and under specific culture conditions. Hence, the identity of true functional site(s) in the CATT haplotype, underlying the association with preclinical atherosclerosis, is not clear.

We and others previously reported associations of PPARGC1A block 2 haplotypes with hypertension and type 2 diabetes mellitus.5,6,23,24 Interestingly, block 2 haplotypes showed no associations with asymptomatic carotid atherosclerosis. Thus, the signaling pathways converging at haplotype blocks 1 and 2 may result in distinct clinical phenotypes, and changes in PGC-1α expression induced by allele-specific effects of promoter SNPs may influence lesion development. Such a mechanism would be consistent with concepts implicating cofactor expression levels as regulators of transcriptional programs.25 In conclusion, if our results are confirmed in other populations, PGC-1α may contribute to the regulation of pathways that influence the risk of atherosclerosis. Because PGC-1α acts at the amplification step of gene expression, only minor functional effects of sequence substitutions may result in phenotypical consequences. Hence, interactions of PPARGC1A SNPs with SNPs in target genes may identify additional members of such a pathway in humans.

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None.

References
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