PGC-1α Gly482Ser Polymorphism Associates With Hypertension Among Danish Whites


Abstract—PGC-1α is a coactivator of numerous transcription factors and is expressed in tissues with high energy demands and abundant in mitochondria. It is induced in the myocardium on fasting and physical exercise, and cardiac-specific overexpression stimulates mitochondrial biogenesis in mice. The common Gly482Ser polymorphism of PGC-1α has previously shown association with arterial hypertension among Austrian men. Thus, we aimed at investigating this relationship in the Danish white population. The Gly482Ser polymorphism was genotyped in a total of 2562 Danish white subjects using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) and a GenoView locked nucleic acid assay (LNA), and the relationships of this variant with blood pressure levels and arterial hypertension were analyzed. Furthermore, we performed a combined analysis of the data from the present study in combination with previously published results. The Ser/Ser genotype was significantly associated with a reduced risk of hypertension and with lower systolic, diastolic, and mean arterial blood pressure levels, predominantly among women. Finally, in a combined analysis using data obtained in both sexes, the Ser/Ser genotype group had an estimated odds ratio of 0.70 (95% confidence interval, 0.56 to 0.86) for hypertension compared with Gly/X carriers (P = 0.001). In conclusion, the Ser allele of PGC-1α Gly482Ser confers a significantly reduced risk of hypertension in whites. Further studies are needed to elucidate the differential role of this polymorphism in men and women. (Hypertension. 2005;45:565-570.)

Key Words: genetics ● hypertension ● diabetes, type 2

Several indices of a genetic basis for hypertension have been derived from family, sibpair, and twin studies. Commonly used methods in the search for genetic loci involved in hypertension and blood pressure regulation include genome scans, through which a range of chromosomal regions have been identified showing linkage with hypertension or levels of systolic or diastolic blood pressure. One of these loci is on chromosome 4p15, where a genomic region spanned by markers D4S2366 and D4S2397 was linked to systolic blood pressure with a lod score of 4.6 after adjustment for age and sex in a Dutch family study. This locus includes the gene PPPARGC1A encoding the coactivator PGC-1α, which is a coactivator of numerous transcription factors including the peroxisome proliferator-activated receptors (PPARs) as well as hepatocyte nuclear factor-4α, nuclear respiratory factors 1 and 2, thyroid hormone receptor, myocyte enhancer factor 2C, and the estrogen receptor-α (ERα). PGC-1α is expressed in a tissue-specific manner and PGC-1α mRNA is found in tissues with high energy demands and abundant in mitochondria such as skeletal muscle, heart, brain, liver, kidney, pancreas, and adipose tissue. In the myocardium, PGC-1α is induced on fasting and physical exercise, and cardiac-specific overexpression of PGC-1α in transgenic mice stimulates mitochondrial biogenesis, leading to loss of sarcomeric structure, decreased contractility, and dilated cardiomyopathy. Moreover, using gene expression profiling a significant downregulation of PGC-1α and PPARα has been observed in the myocardium from transgenic mice with chronic cardiac-specific expression of activated Akt (protein kinase B). Myocardial tissue has a high capacity for fatty acid oxidation, but in states of hypertrophy caused by hypertension, the expression of enzymes involved in fatty acid oxidation is downregulated. Interestingly, various nuclear receptors such as the PPARs, with which PGC-1α interact, are important regulators of components in the fatty acid oxidation pathway.

We have previously identified a frequent substitution of a glycine to a serine amino acid at residue 482 in human PGC-1α, and this polymorphism is reported to be associated with an increased risk of type 2 diabetes mellitus, insulin resistance, and with indices of obesity and altered lipid oxidation. Moreover, the Gly482Ser polymorphism was...
TABLE 1. Clinical and Anthropometrical Characteristics of the 5 Study Populations Enrolled in the Study of the Gly482Ser Polymorphism of PGC-1α

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Study 1 (NGT)</th>
<th>Study 2 (NGT)</th>
<th>Study 3 (NGT)</th>
<th>Study 4 (T2DM)</th>
<th>Study 5 (T1DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (men/women)</td>
<td>1013 (459/554)</td>
<td>210 (94/116)</td>
<td>157 (75/82)</td>
<td>710 (438/272)</td>
<td>472 (256/216)</td>
</tr>
<tr>
<td>Age, y</td>
<td>57 ± 7</td>
<td>39 ± 9</td>
<td>66 ± 5</td>
<td>59 ± 10</td>
<td>47 ± 12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9 ± 4.0</td>
<td>25.5 ± 4.4</td>
<td>25.2 ± 3.8</td>
<td>29.3 ± 5.0</td>
<td>24.3 ± 3.1</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>133 ± 18</td>
<td>117 ± 14</td>
<td>132 ± 20</td>
<td>158 ± 23</td>
<td>134 ± 19</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84 ± 11</td>
<td>74 ± 11</td>
<td>78 ± 10</td>
<td>95 ± 14</td>
<td>77 ± 10</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>43</td>
<td>16</td>
<td>37</td>
<td>83</td>
<td>48</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. Arterial hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or previous or current treatment with blood pressure-lowering drugs.

NGT indicates normal glucose tolerance; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus.

associated with hypertension among Austrian men with the Ser allele conferring a reduction in the prevalence of hypertension.21 This relationship between PGC-1α and blood pressure levels is intriguing because monogenic forms of early-onset hypertension (with severe insulin resistance) relating to heterozygote loss-of-function mutations in PPAR-γ2 (the Val290Met and Pro467Leu substitutions) have been detected.22 It is therefore hypothesized that variation in PGC-1α expression, potentially resulting in altered levels of PGC-1α mRNA expression, may modulate the susceptibility to hypertension. In the present study, we have generated PGC-1α Gly482Ser genotype data in 5 study groups involving a total of 2562 white subjects and investigated the relationship with arterial hypertension and levels of systolic and diastolic blood pressure.

Methods

Study Population

The association studies were performed in: (1) a group of 1013 unrelated glucose-tolerant subjects sampled during 1994 to 2001 from the Danish Central Population Register and at the Research Centre for Prevention and Health;23,24 (2) a group of 210 glucose-tolerant offspring of type 2 diabetic patients ascertained during 1994 to 1997 at Steno Diabetes Center or from the Danish family resource bank at the Department of Human Genetics, University of Copenhagen, Denmark, through 1 type 2 diabetic proband with 4 or more nondiabetic offspring;25 (3) a sample of glucose-tolerant monozygotic and same-sex dizygotic twin pairs sampled through the Danish Twin Registry26 in which 1 twin from each pair (N = 157) was chosen at random to be included in the present study; (4) a group of 710 unrelated type 2 diabetic patients recruited from the outpatient clinic at Steno Diabetes Center during 1994 to 2000 and at the Research Centre for Prevention and Health;24 and (5) a group of 472 unrelated normal controls (urine albumin excretion rate < 30 mg/24 hours) type 1 diabetic patients with a diabetes duration of at least 15 years, recruited at Steno Diabetes Center during 1993 to 2000.27 Clinical characteristics for each study group are listed in Table 1. Diabetes was diagnosed according to 1999 World Health Organization criteria.28 All glucose-tolerant subjects underwent a 75-g oral glucose tolerance test. All participants were Danish whites by self-report. Informed written consent was obtained from all subjects before participation. The study was approved by the Ethical Committee of Copenhagen and was in accordance with the principles of the Declaration of Helsinki.

Laboratory Methods

Blood pressure was measured in the resting state in duplicates or triplicates using a Hawksley random zero mercury sphygmomanometer with an appropriate cuff size. Systolic blood pressure (SBP) was taken at the return of arterial sounds (Korotkoff phase I) and diastolic blood pressure (DBP) at the disappearance of sounds (Korotkoff phase V). Measurements were performed early in the morning before drawing of blood samples and with the participant in a supine position with slightly elevated head. Hypertension was defined as mean SBP ≥ 140 mm Hg and/or mean DBP ≥ 90 mm Hg and/or previous or current treatment with antihypertensive drugs (spironolactone, thiazides, loop diuretics, beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin II receptor blockers, or hydralazine). Overall, 37% of the participants received antihypertensive treatment (men 37%, women 38%), and for none of the 5 study groups did we observe any treatment differences among men and women. Mean arterial blood pressure (MABP) was calculated as mean DBP + one-third × (SBP − DBP).

The genetic analyses were performed on genomic DNA isolated from human leukocytes. The Gly482Ser variant of PGC-1α (EMBL#AF106698) was genotyped using polymerase chain reaction–restriction fragment length polymorphism analysis (study groups 2 to 5) or the GenoView locked nucleic acid assay (study group 1) (please see http://hyper.ahajournals.org for the online supplement methods). No differences in Ser allele frequencies attributable to the 2 genotyping methods were observed.

Statistical Analysis

All genotype groups obeyed the Hardy–Weinberg equilibrium. Data were analyzed both collectively and after stratification according to sex. Fisher exact test was applied to examine differences in allele frequencies between hypertensive and normotensive subjects. The P \( \times \) G test was used to determine the most likely model (dominant, recessive, codominant) for the genotype distributions using Web-Assistent (www.ekstroem.com), which was also used for odds ratio estimations. A combined analysis of all studies was performed using RGui version 1.9.0. Homogeneity between studies was tested assuming a general model \( P = 0.7 \) and a codominant model was tested assuming homogeneity. In the association study of quantitative traits, the genotype and treatment with antihypertensive agents (and sex, when appropriate) entered the model as fixed factors and age and body mass index (BMI) as covariates. Analyses on blood pressure for unrelated subjects were performed using a general linear model in which variables were tested for differences between genotype groups after checking normality of data and homogeneity of variance using Statistical Package for Social Science (SPSS) version 12.0. Blood pressure analyses for related subjects (offspring of diabetic probands, study group 2) were performed using a variance component model with adjustment for familial affiliation using PROC MIXED of the SAS/STAT system version 8.2. \( P < 0.05 \) was considered significant.

Results

Previous studies have shown differences in PGC-1α Gly482Ser allele frequencies depending on glucose tolerance status. Thus, to assess the impact of the Gly482Ser polymorphism on hypertension and individual blood pressure levels, we considered it to be essential that the participants were stratified according to their glucose tolerance. Table 2 gives the results of a case-control study of hypertension among glucose-tolerant subjects (studies 1 and 3), in which
TABLE 2. Allele Frequencies and Distribution of PGC-1α Gly482Ser Genotypes Among Hypertensive and Normotensive Subjects With Normal Glucose Tolerance (Studies 1 and 3)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Study 1</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertensive</td>
<td>Normotensive</td>
</tr>
<tr>
<td>Gly/Gly</td>
<td>210 (48)</td>
<td>244 (42)</td>
</tr>
<tr>
<td>Gly/Ser</td>
<td>183 (42)</td>
<td>259 (45)</td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>43 (10)</td>
<td>74 (13)</td>
</tr>
<tr>
<td>MAF (%)</td>
<td>30.8 (27.8–33.9)</td>
<td>35.3 (32.5–38.0)</td>
</tr>
</tbody>
</table>

Data are number of subjects with each genotype (relative genotype frequency in % within each group). MAF indicates minor allele frequency in % (95% CI); OR, odds ratio (95% CI).

we observed a higher frequency of the Ser allele among the normotensive subjects as compared with the hypertensive subjects ($P=0.04$ and 0.07 for studies 1 and 3, respectively). In addition, the Ser/Ser genotype was less frequent in the groups of hypertensive subjects. This relationship was evident only among women, eg, with $P=0.02$ and 0.01 for allele and genotype frequencies, respectively, in study 1 of 554 women (data not shown). The same tendencies were observed for patients with type 2 diabetes, in which the Ser allele frequencies were 36.7% (95% confidence interval [CI], 33.9 to 39.5) and 38.2% (32.1 to 44.4) among hypertensive and normotensive participants for the group of both sexes and 37.8% (33.4 to 42.3) and 43.9% (33.2 to 54.6) for the women, respectively. For study 5, no relationships of Gly482Ser genotype distribution and/or allele frequency with hypertension was observed ($P=0.8$ and 0.9, data not shown). The genotype data in Table 2 were tested in a dominant, codominant, recessive, and a general model. We observed that with the given genotype distributions among affected and unaffected subjects, respectively, the most likely model for the penetrance of the Gly and Ser alleles is when the combined group of Gly/Gly and Gly/Ser carriers is compared with the Ser/Ser carriers, although other models are applicable except from a model combining the Gly/Ser and Ser/Ser genotypes. For the women in study 1, the recessive genetic model of data interpretation results in an odds ratio (OR) of 0.47 (95% CI, 0.25 to 0.87; $P=0.01$) for risk of hypertension compared with the Gly/X genotypes (X being either Gly or Ser). This genotype distribution model was subsequently used in our investigation of blood pressure levels in studies 1 to 5 (Table 3 and data not shown). Here, we found that Gly/X carriers had significantly higher systolic and mean arterial blood pressure

TABLE 3. Clinical and Anthropometrical Characteristics of Study Participants Stratified According to PGC-1α Gly482Ser Genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gly/X</th>
<th>Ser/Ser</th>
<th></th>
<th>Gly/X</th>
<th>Ser/Ser</th>
<th></th>
<th>Gly/X</th>
<th>Ser/Ser</th>
<th></th>
<th>Gly/X</th>
<th>Ser/Ser</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>N=896</td>
<td>N=117</td>
<td>P</td>
<td>N=190</td>
<td>N=20</td>
<td>P</td>
<td>N=132</td>
<td>N=25</td>
<td>P</td>
<td>N=607</td>
<td>N=103</td>
<td>P</td>
</tr>
<tr>
<td>Age, y</td>
<td>57±7</td>
<td>57±7</td>
<td>40±9</td>
<td>38±8</td>
<td>25±3.8</td>
<td>25±3.8</td>
<td>97±12</td>
<td>91±9</td>
<td>0.02</td>
<td>117±15</td>
<td>114±18</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9±3.9</td>
<td>26.0±4.4</td>
<td>25.6±4.4</td>
<td>24.5±4.1</td>
<td>25.1±3.8</td>
<td>25.8±3.7</td>
<td>29.4±5.1</td>
<td>28.9±4.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134±18</td>
<td>130±17</td>
<td>0.01</td>
<td>118±14</td>
<td>111±13</td>
<td>0.1</td>
<td>134±20</td>
<td>126±19</td>
<td>0.1</td>
<td>159±23</td>
<td>156±24</td>
<td>0.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84±11</td>
<td>83±11</td>
<td>0.2</td>
<td>74±10</td>
<td>71±12</td>
<td>0.6</td>
<td>79±10</td>
<td>74±7</td>
<td>0.01</td>
<td>96±13</td>
<td>93±16</td>
<td>0.08</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>101±12</td>
<td>99±12</td>
<td>0.04</td>
<td>89±11</td>
<td>84±11</td>
<td>0.4</td>
<td>97±12</td>
<td>91±9</td>
<td>0.02</td>
<td>117±15</td>
<td>114±18</td>
<td>0.07</td>
</tr>
<tr>
<td>Men</td>
<td>N=401</td>
<td>N=58</td>
<td>N=87</td>
<td>N=7</td>
<td>N=63</td>
<td>N=12</td>
<td>N=383</td>
<td>N=55</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>58±7</td>
<td>58±7</td>
<td>39±9</td>
<td>39±12</td>
<td>67±4</td>
<td>63±6</td>
<td>58±10</td>
<td>58±9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3±3.3</td>
<td>26.7±3.6</td>
<td>25.7±3.8</td>
<td>26.5±4.5</td>
<td>25.1±3.0</td>
<td>24.6±3.0</td>
<td>29.3±5.0</td>
<td>28.0±4.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>135±17</td>
<td>133±15</td>
<td>0.3</td>
<td>120±14</td>
<td>121±9</td>
<td>0.9</td>
<td>136±21</td>
<td>128±18</td>
<td>0.6</td>
<td>156±22</td>
<td>157±27</td>
<td>0.6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>86±10</td>
<td>86±10</td>
<td>0.7</td>
<td>75±11</td>
<td>74±15</td>
<td>0.8</td>
<td>81±11</td>
<td>74±9</td>
<td>0.07</td>
<td>96±13</td>
<td>94±17</td>
<td>0.6</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>102±11</td>
<td>101±11</td>
<td>0.9</td>
<td>90±11</td>
<td>90±12</td>
<td>0.9</td>
<td>99±13</td>
<td>92±11</td>
<td>0.2</td>
<td>116±15</td>
<td>115±19</td>
<td>0.9</td>
</tr>
<tr>
<td>Women</td>
<td>N=495</td>
<td>N=59</td>
<td>N=103</td>
<td>N=13</td>
<td>N=69</td>
<td>N=13</td>
<td>N=224</td>
<td>N=48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>57±7</td>
<td>56±8</td>
<td>40±8</td>
<td>37±5</td>
<td>65±5</td>
<td>66±5</td>
<td>60±10</td>
<td>63±10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6±4.4</td>
<td>25.4±4.9</td>
<td>25.6±4.8</td>
<td>23.4±3.5</td>
<td>25.1±4.5</td>
<td>26.8±4.1</td>
<td>29.5±5.2</td>
<td>29.9±5.4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>133±19</td>
<td>127±18</td>
<td>0.01</td>
<td>116±14</td>
<td>106±11</td>
<td>0.08</td>
<td>131±20</td>
<td>125±20</td>
<td>0.1</td>
<td>162±24</td>
<td>156±22</td>
<td>0.006</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83±11</td>
<td>81±10</td>
<td>0.1</td>
<td>73±10</td>
<td>69±10</td>
<td>0.7</td>
<td>77±9</td>
<td>74±6</td>
<td>0.1</td>
<td>95±14</td>
<td>92±16</td>
<td>0.06</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>100±13</td>
<td>96±12</td>
<td>0.04</td>
<td>87±11</td>
<td>81±9</td>
<td>0.3</td>
<td>95±12</td>
<td>91±8</td>
<td>0.07</td>
<td>118±16</td>
<td>113±16</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are means±SD. All P values were adjusted for age, sex, and BMI and compare Gly/X carriers with Ser/Ser carriers.
among the unrelated glucose-tolerant subjects of study 1 and significantly higher diastolic and mean arterial blood pressure in the sample of monozygotic and dizygotic twins (study 3). Moreover, we demonstrated borderline significantly higher diastolic and mean arterial blood pressure levels among the Gly/X type 2 diabetic patients of study 4. Among the type 1 diabetic patients of study 5 and among the offspring of type 2 diabetic probands (study 2), there were no associations of blood pressure levels with genotype (Table 3 and data not shown). We stratified all study groups according to sex and observed that the associations were most apparent among women (Table 3), although the male twins (study 3) had borderline significantly altered diastolic blood pressure. Finally, we performed a combined analysis of our case-control studies (studies 1, 3, 4, and 5) along with the previously published results derived from studies of Austrian subjects (Figure 1). All data were from the combined groups of both sexes and again we observed that a dominant model for the Ser allele was regarded as unlikely (P = 0.005). In a recessive model, the Gly482Ser polymorphism was significantly associated with hypertension (P = 0.001; OR, 0.70) (0.56 to 0.86) for Ser/Ser compared with Gly/X, and in a codominant model the OR was 0.85 (0.76 to 0.94) (P = 0.001).

Discussion

There is substantial evidence for the existence of both monogenic and polygenic forms of essential hypertension, although these are believed to be modulated by both gene–environment and gene–gene interactions. A recent report of association between the PGC-1α Gly482Ser polymorphism and hypertension along with genetic linkage studies and investigations of the expression and coactivation functions of PGC-1α prompted us to examine the relationship between the Gly482Ser polymorphism and hypertension and levels of systolic and diastolic blood pressure in 5 groups of thoroughly characterized subjects.

Because of reports of association of the codon 482 variant with diabetes, stratification of the participants according to glucose tolerance status was necessary. Furthermore, all statistical analyses of blood pressure were undertaken with adjustment for body size as assessed by BMI. If BMI interacts with the genetic mechanism encoded by the Gly482Ser polymorphism, this poses a potential risk given that the adjustment of blood pressure for covariation in BMI would weaken the blood pressure variation attributable to genetic variation and thereby limit the power of the data. Contrary, a lack of appropriate adjustments could result in false-positive observations. Findings of an association of the PPARGC1A codon 482 variant with obesity indices have been reported. To circumvent this problem, adjustment was made for BMI in the analyses of blood pressure, whereas the case-control studies of hypertension as a qualitative trait were performed in groups with matched BMI.

In the present study, we were able to replicate the previous findings by Oberkofler et al in the sense that we too observed a lower frequency of the Ser allele and the Ser/Ser genotype among hypertensive subjects. Surprisingly, whereas the previous observations were made predominantly among men, our findings point toward a role of the PPARGC1A locus mainly among women, but also in the combined groups of both sexes. In our case-control study of hypertension (Table 2), the association of the Ser allele frequency with hypertension was present in a total of 1013 subjects of both sexes. After stratification according to sex, we observed that the association was far more marked in women. Contrary, in the study of mean blood pressure levels and relationships to Gly482Ser genotype (Table 3), we did observe some suggestive support of a role of the Ser allele in hypertension among men, although the findings among women were still more persuasive. The suggestive findings in studies 2 and 3 are probably limited by the relatively low number of participants and the resulting low power to detect blood pressure differences in these groups. Furthermore, the number of tests performed in the present study should be considered when interpreting the results as no adjustment for multiple testing was performed. In summary, even though the 5 individual studies of blood pressure levels were not consistent and each provided a relatively low statistical power, they all pointed in the same direction: toward lower systolic and diastolic blood pressure levels in subjects who had the Ser/Ser genotype. Our results contrast a French study in which the Ser/Ser versus Gly/Gly genotype had an OR of 2.52 for hypertension among men, whereas no association was observed among women. This discrepancy may be caused by the low sample size in the French study (eg, 253 women, of which 73% were hypertensive, yielding 185 cases and 68 control subjects).

In studies 4 and 5, there were no statistically significant relationships between PGC-1α Gly482Ser genotype and hypertension. However, because of the high prevalence of hypertension, especially among type 2 diabetic patients, and the resulting low number of normotensive diabetic patients, this part of our investigation (study group 4) is of an insufficient size. Thus, we performed a combined analysis of studies 1, 3, 4, 5, and the reported data from Oberkofler et al. As can be observed from Figure 1, Ser/Ser carriers had a significantly reduced risk of hypertension as compared with Gly/Gly carriers.

One possible explanation for the disparity in the relationship between hypertension and PGC-1α variation among men and women may be provided by the relationship between PGC-1α expression and the function of the ERs, which are differentially expressed in men and women. ERα and ERβ are members of the steroid/thyroid hormone receptor superfamily and are nuclear proteins regulating the transcription of specific target genes. Estrogens may limit atherogenesis in premenopausal women, whereas clinical trials have not been able to confirm this under administration of estrogen replacement therapy in postmenopausal women. However, although the mechanisms may be unclear, numerous epidemiological studies have indicated a significantly lower relative risk of ischemic cardiovascular disease among women. This finding may be partially accounted for by the ability of estrogen to reduce total serum cholesterol levels, specifically the more atherogenic low-density lipoprotein cholesterol, by direct effects of estrogen on the vasculature via the nitric oxide systems, in which an increase in nitric oxide has been suggested to prevent adhesion of monocytes to endothelial cells, or through a reduction of Ca2+ channel activity. Intriguingly, variation in the genes encoding the ERs has been
suggested to associate with hypertension and cardiovascular disease in general.32–35 Moreover, PGC-1α is a coactivator of ERα.5,7 Therefore, in future studies there is an obvious need to test the influence of the putative gene–gene interaction between variants in the genes encoding the discussed vasoactive hormones. Likewise, PGC-1α interacts with the nuclear receptor estrogen-related receptor α in inducing mitochondrial biogenesis in tissues with high energy demand like heart, kidney, and muscle in response to physical exercise, fasting, and exposure to cold.36–38 In vitro, PGC-1α induces ESRRA (the gene encoding estrogen-related receptor α) promoter activity dependent on a polymorphic 23-bp DNA sequence, which is present in variable copy number,39 and it is likely that similar interdependent gene–gene relations may be operative between PGC-1α polymorphisms and genetic variation in other components of a common pathway involved in the modulation of blood pressure.

It is puzzling that the Ser allele apparently is associated with a decreased risk of hypertension, a disease that is commonly associated with type 2 diabetes, considering that the codon 482 Ser allele of PGC-1α also associates with an increased risk of type 2 diabetes in the same populations.17 Nevertheless, the same phenomenon was reported in the Austrian population, in which carriers of a haplotype consisting of the Ser allele and none of 3 other minor alleles in a specific haplotype block were observed among type 2 diabetic patients but not among control subjects.40 It also remains to be shown whether the Gly482Ser polymorphism per se is the functional variant or it is a marker of a yet unidentified variation in this gene locus that impacts on risk of diabetes and hypertension.

In conclusion, in both individual study populations and in a combined analysis of white subjects, we demonstrate that the Ser allele of PGC-1α at codon 482 in its homozygous form is associated with reduced levels of systolic and diastolic blood pressure and a decreased risk of arterial hypertension. Because of the relatively high frequency of the Gly482Ser among whites, this variant may have a considerable effect at the population level.

Perspectives
Even though hypertension and type 2 diabetes often coexist, the present findings point to the presence of genetic variation that tends to confer a divergence of these 2 phenotypes. More complex mechanisms than regarding hypertension as a complication of type 2 diabetes and/or insulin resistance may be involved, and further studies are needed to elucidate these potentially divergent pathways. More individualized treatment strategies based on genetic polymorphisms that serve as markers for an increased risk of hypertension may be implemented or modified. Moreover, a continuous effort to elucidate the pathophysiology underlying hypertension and cardiovascular disease may benefit from a detailed characterization of the genetic background of hypertension and metabolic diseases in general.
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