G-Protein β₃-Subunit Gene 825T Allele and Hypertension
A Longitudinal Study in Young Grade I Hypertensives

Michelangelo Sartori, Andrea Semplicini, Winfried Siffert, Paolo Mormino, Alberto Mazzer, Fabrizio Pegoraro, Lucio Mos, Mikolaj Winnicki, Paolo Palatini

Abstract—The 825T allele of the GNB3 gene has been associated with essential hypertension and obesity in cross-sectional studies. We have therefore planned a longitudinal cohort study to assess whether the GNB3 825T allele is predictive of blood pressure increase in young subjects with grade I hypertension. We genotyped at the GNB3 825 locus 461 participants of the Hypertension and Ambulatory Recording Venetia Study (HARVEST) study (age, 18 to 45 years) at low cardiovascular risk, according to 1999 ISH/WHO criteria. The study end point was eligibility for antihypertensive medication, that is, progression to grade II hypertension during the first year of observation or office systolic blood pressure ≥150 mm Hg and/or office diastolic blood pressure ≥95 mm Hg in two later consecutive visits during follow-up. At baseline, there was no statistically significant difference among genotypes with respect to body mass index, blood pressure, and heart rate. During follow-up (mean, 4.7 years), 113 (51.1%) patients with CC genotype and 145 (60.4%) patients with TT/TC genotype reached the end point. According to survival analysis, the patients carrying the 825T allele had an increased risk of reaching the blood pressure end point (CI, 1.108 to 1.843; \( P = 0.006 \)). In young patients with grade I hypertension, the 825T allele is associated with increased risk of progression to more severe hypertension requiring antihypertensive therapy. The GNB3 825T allele may be considered a genetic marker of predisposition for hypertension. (Hypertension. 2003;42:909-914.)

Key Words: blood pressure monitoring, ambulatory ■ genetics ■ antihypertensive therapy ■ hypertension, genetic ■ signal transduction ■ GTP-binding proteins

Both genetic and environmental factors contribute to the pathogenesis of essential hypertension. Hypertension is about twice as common in subjects who have one or two hypertensive parents, and many epidemiological studies suggest that genetic factors account for approximately 30% of the variation in blood pressure in various populations. Polymorphisms in several genes has been associated with blood pressure levels. Siffert et al described a C825T polymorphism in the GNB3 gene encoding the β-subunit of heterotrimeric G proteins, with the 825T allele being associated with alternative splicing of the gene, hypertension, and increased body mass index (BMI). The 825T allele has been shown to be associated also with diastolic dysfunction, increased left ventricular mass index, and increased risk for left ventricular hypertrophy in patients with hypertension. However, the association of T allele with hypertension and other cardiovascular risk factors has been disputed in recent studies. A large cross-sectional study could not show association between GNB3 genotypes and left ventricular hypertrophy. Hengstenberg and coworkers confirmed the association between the 825T allele and hypertension, whereas Snapir et al produced negative results. However, in that latter study, the number of 825T allele carriers was remarkably low.

All the previous studies selected patients from a large-scale, population-based sample, pooling together normotensive subjects, hypertensive patients, and patients taking antihypertensive medications. Moreover, all but one study were cross-sectional and included patients with a broad range of age and cardiovascular risks.

The GNB3 polymorphism has never been formally tested as a potential marker of risk for development of hypertension, and up to now it is unclear to what extent the 825T allele has a direct effect on blood pressure, independent of body weight and other potential confounders such as age and drug treatment. Therefore, to avoid the effect of these confounders on blood pressure, we studied a homogeneous cohort of young, never-treated patients with stage I hypertension. The aim of our study was to investigate in these subjects whether the 825T allele was associated with increased risk of development of more severe hypertension during long-term follow-up.
Methods

Study Population
The study was carried out in 461 white patients with grade I hypertension at low cardiovascular risk from hypertension clinics in northeast Italy, which took part in the multicenter Hypertension and Ambulatory Recording Venetia Study (HARVEST) study, a trial on the predictive value of ambulatory blood pressure for the development of essential hypertension in patients with borderline to mild hypertension. Briefly, inclusion criteria were described previously. Inclusion criteria were age 18 to 45 years, supine diastolic blood pressure ranging from 90 to 99 mm Hg and/or supine systolic blood pressure from 140 to 159 mm Hg, and no previous antihypertensive medication. The baseline data included a medical and family history and a questionnaire on current cigarette smoking and alcohol intake, according to a procedure previously reported. The interview was performed by the local investigator (physician). Coffee consumption was defined according to the number of caffeine-containing coffees drunk per day. The caffeine content per cup of Italian coffee averages 100 mg. Subject were categorized as non-drinkers (0 cups per day), moderate drinkers (1 to 3 cups per day), and heavy drinkers (>3 cups per day). Tea drinking was not taken into account, being unusual and irregular in this area of Italy. Current smokers were those who reported smoking 1 or more cigarettes per day and were divided into 3 categories, according to whether they smoked 1 to 5, 6 to 10, or >10 cigarettes per day. Alcohol intake was calculated by summing the total number of milliliters of alcohol consumed as wine, beer, and liqueurs. Categories of alcohol intake were nondrinkers, <50 g, 50 to 100 g, and >100 g of alcohol per day. For physical activity habits, subjects were categorized as nonexercisers if they did not perform any sport activity on a regular basis and exercisers if they had performed the above-mentioned sports at least once in a week during the previous 2 months.

All participants underwent a physical examination, anthropometric measurements, office (mean of 3 readings) and 24-hour noninvasive ambulatory blood pressure (ABPM) measurement, resting ECG, and echocardiography. Diabetes was ruled out by fasting serum glucose test and renal impairment by serum creatinine and urinalysis. None of the patients had cardiac failure or evidence of coronary heart disease.

The study was approved by the HARVEST Ethics Committee, and informed consent was obtained from all participants.

Study Protocol
The subjects taking part in this subproject were all those recruited and followed up in 4 of the participating centers who gave informed consent to blood sampling for genetic studies. After enrollment, the patients were seen in the outpatient clinic monthly during the first 3 months of follow-up, after 6 months, after 1 year, and every 6 months thereafter. At each visit, office blood pressure was measured by the local investigator (physician) according to the recommendations of the British Society of Hypertension. The mean of 3 readings taken in the supine position was taken. Phase V Korotkoff sound was considered as diastolic blood pressure, except in subjects with sound tending to zero, in whom phase IV was taken. For the present study, the end point was eligibility for antihypertensive medication, that is, progression to grade II hypertension (supine office systolic blood pressure ≥160 mm Hg and/or supine office diastolic blood pressure ≥100 mm Hg) during the first year of follow-up or supine office systolic blood pressure ≥150 mm Hg and/or supine office diastolic blood pressure ≥95 mm Hg in two consecutive visits later on, in accordance with 1999 ISH/WHO guidelines for patients at low cardiovascular risk such as the participants in the present study. ABPM was obtained with either A&D TM-2420 model 7 (A&D Co) or with the ICR Spacelabs 90207 (Spacelabs Inc). Both of these devices were previously validated. ABPM was performed at enrollment, after 5, 8, and 10 years, unless the patient reached the end point and was qualified for antihypertensive treatment.

M-mode and 2-dimensional echocardiography was carried out in a subgroup of the study cohort, as previously described. Briefly, left ventricular internal diameter and wall thickness were measured at end-diasole, according to recommendation of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated according to the following formula:

\[ \text{LVM (g)} = 0.8 \times (\text{IVST} + \text{LVDD} + \text{PWT})^3 - \text{LVDD}^3 + 0.6, \]

where IVST is the interventricular septum thickness in diastole, LVDD is the left ventricular end-diastolic diameter, and PWT is the posterior wall thickness in diastole. To correct for differences in body size, left ventricular mass was normalized to body surface area (LVMI). The relative wall thickness ratio was calculated as IVST+PWT/LVDD. All measurements were taken by two experienced physicians, independent from each other, according to a procedure described elsewhere. The intraobserver and interobserver variability was between 1.5% and 3% for the various M-mode variables.

Genotyping
Genomic DNA was extracted from whole blood with a proprietary reagent (QiAMP, Qiagen), according to the manufacturer’s protocol. For determination of GNB3 C825T allele status, the laboratory procedure was slightly modified from that previously published, as it yielded more PCR products. Briefly, PCR was performed with the primers 5’-GCT GCC CAG TGC TGA TCC C-3’ (sense) and 5’-TGG GGA GGG TCC TTC CAG C-3’ (antisense). PCR reactions began with denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C (30 seconds), annealing at 63°C (30 seconds), extension at 72°C (1 minute), and a final extension at 72°C (7 minutes). PCR products were restricted with 0.5 U BsdI (Fermentas), separated on 2.5% agarose gels and visualized under UV illumination. The TT genotype yields one unrestricted band of 313 bp. Complete restriction (CC genotype) generates bands of 142 and 171 bp.

Statistical Analysis
Analysis was carried out with the use of the SPSS software package (version 10.0.1; SPSS Inc). Relations between variables were assessed by means of the Pearson correlation for continuous variables and \( \chi^2 \) or Fisher exact test for categorical variables. The Student \( t \) test and univariate analysis of variance with Bonferroni correction for multiple comparisons were used to compare means among alleles. Hardy-Weinberg equilibrium was assessed by \( \chi^2 \) test with 1 degree of freedom. Cumulative end point curves were estimated with the Kaplan-Meier procedure, and the effect of the T allele on the end point was estimated from multivariate Cox proportional hazard models. The significance level was set to \( \alpha = 0.05 \). Results are given as mean±SEM.

Results
Among these 461 hypertensive patients, 221 (47.9%) were homozygous for the 825 C allele (CC genotype), 205 (44.5%) were heterozygous (TC genotype), and 35 (7.6%) were homozygous for the 825 T allele (TT genotype). The genotype distribution was in Hardy-Weinberg equilibrium. The three groups did not differ with regard to age, gender, BMI (Table 1). No significant difference between the three groups was also observed with regard to smoking, ethanol consumption, and physical activity (data not shown). On the contrary, those with CT genotype had lower serum creatinine in comparison with those with CC genotype and those with CC genotype lower fasting glucose in comparison with the other groups (Table 1).

At enrollment, there was no significant difference between the patients with CC genotype and those with TC and TT genotypes with respect to office blood pressure values and ambulatory blood pressure values (Table 1). Heart rate was also similar among the three groups (Table 1).
**TABLE 1. Baseline Characteristics of the Study Population According to GNB3 Genotype**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CC (n=221)</th>
<th>CT (n=205)</th>
<th>TT (n=35)</th>
<th>P*</th>
<th>CT+TT (n=240)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F, n</td>
<td>156/65</td>
<td>153/52</td>
<td>28/7</td>
<td>0.406</td>
<td>181/59</td>
<td>0.243</td>
</tr>
<tr>
<td>Age, y</td>
<td>33.2±0.6</td>
<td>33.1±0.6</td>
<td>33.3±0.2</td>
<td>0.993</td>
<td>33.1±0.5</td>
<td>0.979</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.3±0.3</td>
<td>25.4±0.2</td>
<td>24.5±0.6</td>
<td>0.372</td>
<td>25.2±0.2</td>
<td>0.934</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>146.8±0.7</td>
<td>146.4±0.8</td>
<td>146.9±1.7</td>
<td>0.931</td>
<td>146.5±0.7</td>
<td>0.764</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>93.6±0.4</td>
<td>93.2±0.4</td>
<td>93.2±1.1</td>
<td>0.763</td>
<td>93.2±0.5</td>
<td>0.463</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>76.4±0.7</td>
<td>76.2±0.7</td>
<td>73.2±1.6</td>
<td>0.194</td>
<td>75.7±0.7</td>
<td>0.457</td>
</tr>
<tr>
<td>SBP 24 h, mm Hg</td>
<td>130.5±0.7</td>
<td>130.5±0.8</td>
<td>131.8±1.4</td>
<td>0.797</td>
<td>130.7±0.7</td>
<td>0.851</td>
</tr>
<tr>
<td>DBP 24 h, mm Hg</td>
<td>81.4±0.5</td>
<td>80.7±0.5</td>
<td>79.2±1.4</td>
<td>0.254</td>
<td>80.5±0.5</td>
<td>0.192</td>
</tr>
<tr>
<td>HR 24 h, bpm</td>
<td>72.9±0.5</td>
<td>72.3±0.6</td>
<td>72.9±1.6</td>
<td>0.737</td>
<td>72.4±0.6</td>
<td>0.526</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.6±0.1</td>
<td>14.5±0.1</td>
<td>14.7±0.3</td>
<td>0.815</td>
<td>14.6±0.09</td>
<td>0.741</td>
</tr>
<tr>
<td>Erythrocyte count, 10¹²/L</td>
<td>4.95±0.04</td>
<td>4.91±0.04</td>
<td>5.10±0.08</td>
<td>0.174</td>
<td>4.95±0.04</td>
<td>0.941</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.93±0.02</td>
<td>0.86±0.02</td>
<td>0.94±0.15</td>
<td>0.002</td>
<td>0.87±0.01</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>91.8±0.8</td>
<td>95.0±0.9</td>
<td>97.1±2.3</td>
<td>0.004</td>
<td>95.3±0.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>197.9±3.0</td>
<td>194.4±2.9</td>
<td>210.0±6.4</td>
<td>0.120</td>
<td>196.7±2.7</td>
<td>0.748</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>55.4±1.3</td>
<td>52.0±1.1</td>
<td>51.5±2.8</td>
<td>0.110</td>
<td>51.9±1.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>113.1±5.6</td>
<td>105.3±4.9</td>
<td>109.2±12.3</td>
<td>0.575</td>
<td>105.8±4.5</td>
<td>0.310</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.1±0.1</td>
<td>5.0±0.1</td>
<td>5.1±0.2</td>
<td>0.721</td>
<td>5.0±0.1</td>
<td>0.448</td>
</tr>
<tr>
<td>AER, mg/24 h</td>
<td>11.5±1.8</td>
<td>9.6±1.3</td>
<td>10.3±2.5</td>
<td>0.697</td>
<td>9.7±1.2</td>
<td>0.405</td>
</tr>
</tbody>
</table>

Values are mean±SEM. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; HDL, high-density lipoprotein; and AER, albumin excretion rate. CC, CT, TT, and CT+TT refer to genotype groups described in this study.

*The statistical analysis was performed by analysis of variance among the 3 genotypes.
†The statistical analysis was performed by Student t test for CT+TT vs CC genotypes.

According to studies on the biological effect of GNB3 825T allele, the presence of one 825T allele is sufficient for the expression of the Gβ3 splice variant. G-protein activation is increased to a similar extent, and the associated cellular phenotypes, like chemotaxis, agonist-induced vasoconstriction, and epinephrine-induced platelet aggregation, are virtually identical in cells with TC or TT genotype but increased in comparison with those with CC genotype. For these reasons and because the TT genotype is relatively rare in white populations, in previous studies patients homozygous or heterozygous (TT and TC genotypes, respectively) were combined for analysis. No difference was seen between CT and TT groups for any parameter in the present study. Therefore, GNB3 C825T polymorphism was categorized as a binomial variable according to the absence or presence of a T allele, respectively. Serum creatinine and HDL cholesterol were lower in the patients carrying the T allele in comparison with those with CC genotype, whereas fasting glucose was higher (Table 1).

In 350 subjects, echocardiographic parameters were available and are displayed in Table 2, according to the presence or absence of the 825T allele. In agreement with a previous report, patients with CT/TT genotype, compared with those with CC genotype, had a significantly increased LVMI (93.1±1.2 versus 89.5±1.2 g/m², P=0.031).

**TABLE 2. Echocardiographic Characteristics of the Study Population According to Genotype**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CC (n=164)</th>
<th>CT (n=159)</th>
<th>TT (n=27)</th>
<th>P*</th>
<th>CT+TT (n=186)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVST, mm</td>
<td>9.5±0.1</td>
<td>9.6±0.1</td>
<td>9.6±0.2</td>
<td>0.701</td>
<td>9.6±0.1</td>
<td>0.436</td>
</tr>
<tr>
<td>Diastolic PWT, mm</td>
<td>8.9±0.1</td>
<td>9.0±0.1</td>
<td>9.1±0.2</td>
<td>0.554</td>
<td>9.0±0.1</td>
<td>0.282</td>
</tr>
<tr>
<td>Diastolic LV diameter, mm</td>
<td>51.2±0.4</td>
<td>51.8±0.3</td>
<td>51.4±0.9</td>
<td>0.422</td>
<td>51.7±0.3</td>
<td>0.212</td>
</tr>
<tr>
<td>Systolic PWT, mm</td>
<td>15.0±0.2</td>
<td>15.1±0.4</td>
<td>15.2±0.5</td>
<td>0.832</td>
<td>15.1±0.2</td>
<td>0.620</td>
</tr>
<tr>
<td>Systolic LV diameter, mm</td>
<td>33.3±0.4</td>
<td>34.2±0.3</td>
<td>32.9±0.8</td>
<td>0.121</td>
<td>34.0±0.3</td>
<td>0.127</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>89.5±1.2</td>
<td>93.2±1.3</td>
<td>93.1±3.1</td>
<td>0.090</td>
<td>93.1±1.2</td>
<td>0.031</td>
</tr>
<tr>
<td>EF, %</td>
<td>63.7±0.6</td>
<td>62.3±0.6</td>
<td>65.1±1.3</td>
<td>0.081</td>
<td>62.7±0.6</td>
<td>0.205</td>
</tr>
</tbody>
</table>

Values are mean±SEM. IVST indicates interventricular septum thickness; PWT, posterior wall thickness; LV, left ventricular; LVMI, left ventricular mass index; and EF, ejection fraction.

*The statistical analysis was performed by analysis of variance among the 3 genotypes.
†The statistical analysis was performed by Student t test for CT+TT vs CC genotypes.
During follow-up, the target end point developed in 258 patients (grade II hypertension during the first year of follow-up or office systolic blood pressure ≥150 mm Hg and/or office diastolic blood pressure ≥95 mm Hg, in two consecutive visits, later on): 113 (51.1%) in the group with CC genotype, 126 (61.5%) in those with the TC genotype, and 19 (54.3%) in those with the TT genotype allele. At the end of follow-up there was no significant difference between the patients with CC genotype and those with TC and TT genotypes with respect to BMI, office and ambulatory blood pressure, and heart rate (Table 3).

The Kaplan-Meier estimated curves of probability of reaching the end point according to the presence/absence of T allele are shown in the Figure. Cumulative end point curves were significantly different (P=0.021) and indicate that the patients with CT + TT genotype progress to a more severe hypertension earlier than those with CC genotype. This is also suggested by the finding that average follow-up time was significantly different in patients carrying the T allele (Table 3).

According to the multivariate Cox model, presence of the T allele (95% CI, 1.108 to 1.843; P=0.006), 24-hour mean systolic blood pressure (95% CI, 1.013 to 1.040; P<0.001), 24-hour mean diastolic blood pressure (95% CI, 1.007 to 1.049; P=0.009), BMI (95% CI, 1.022 to 1.099; P=0.002), and age (95% CI, 1.008 to 1.042; P=0.004) at enrollment were predictors of reaching the end point, whereas male gender, 24-hour heart rate, physical inactivity, smoking habit, and alcohol intake were not (Table 4).

### Discussion

The present longitudinal study demonstrates that the GNB3 825T allele is associated with a greater blood pressure increase and more frequent need of antihypertensive therapy in an homogeneous cohort of nonobese, young, never-treated, grade I hypertensive patients during a mean follow-up time of 4.7 years. Therefore, this polymorphism may be regarded as an indicator of the need for drug treatment in patients with mild hypertension and as a risk marker for development of severe and complicated hypertension, since it has been associated also with obesity, increased left ventricular mass, carotid atherosclerosis, and insulin resistance syndrome.

In vitro studies have shown that the GNB3 825T allele is associated with alternative splicing, giving rise to a Gβ3...
protein that lacks 41 amino acids. Heterotrimeric G proteins couple transmembrane receptors to intracellular second messengers. The 825T allele is associated with enhanced signal transduction and cell proliferation mediated by pertussis toxin-sensitive G proteins in lymphoblasts and fibroblasts from selected patients with essential hypertension. In neutrophils, the splice variant of the Gβ3 protein increases chemotaxis. In platelets, aggregation after epinephrine and after the combination of epinephrine and ADP was significantly enhanced in carriers of the 825T allele. Increased G-protein activation is not only observed in vitro but also in cells studied ex vivo. Baumgart et al have shown in vivo an increased constriction of coronary arteries after a bolus intravenous injection of an α2-adrenoceptor-activating compound in 825T allele carriers. Furthermore, vasoconstriction in response to endothelin-1, angiotensin II, and noradrenaline was significantly enhanced in the skin microcirculation in healthy carriers of the 825T allele. Thus, the association of the 825T allele with earlier increase in blood pressure over time reported here appears not to be fortuitous.

Several studies have tested the hypothesis that the 825T allele is associated with hypertension, and such an association has been reported in various populations. Cross-sectional studies showed an association in population samples from Germany, Poland, Australia, and in blacks (Caribbean and West Africans) from the United Kingdom. However, in patients from Europe, further studies have shown no association between the 825T allele and hypertension. Similarly, no association was found in populations from Asia and in blacks in the United States. It must be noted that most of these studies have important limitations. First, all included a significant number of patients who were receiving pharmacological treatment. Recently, the TT genotype has been shown to be a significant predictor of greater decline in systolic and diastolic blood pressures after hydrochlorothiazide therapy, and this may have diluted the relation between genotype and blood pressure. Furthermore, they were cross-sectional or retrospective case-control studies with one exception, they included normotensive and hypertensive patients, and the definition of hypertension and cardiovascular risk profile varied among studies. Only longitudinal studies in a well-defined cohort may define the predictive power of a genotype. A prospective, population-based study did not report any association between the 825T allele and hypertension. However, this study was conducted in an older population from Finland with high coronary morbidity and mortality rates, and it included both normotensive and hypertensive patients, some of them taking antihypertensive drugs.

To avoid all these potential biases, we designed a prospective study in a homogenous cohort with a narrow range of blood pressure levels at baseline. Moreover, the patients enrolled in the HARVEST study are nonobese and have never been treated for hypertension. We reasoned that in these young hypertensive patients with low cardiovascular risk profile, the genetic influences on blood pressure could be more pronounced than in obese, older patients with long-lasting hypertension, in whom the effects of environmental factors may prevail.

National health surveys have found hypertension to be present in 15% to 25% of the adult population. The majority of individuals had mild-to-borderline hypertension, with at least two thirds having a diastolic blood pressure between 90 and 104 mm Hg. Only 3.8% per year progress to more severe hypertension. Therefore, a risk indicator of progression to more severe hypertension may be useful for the early identification of those at the highest cardiovascular risk, who may profit from an early pharmacological treatment.

The results of the present study show that the 825T allele of GNB3 gene is associated with earlier blood pressure increase and a more frequent need of antihypertensive therapy during a mean follow-up of 4.7 years. This explains in part why more severe hypertension develops only in some patients with mild hypertension. Therefore, genotyping the GNB3 polymorphism may help to identify those hypertensive patients who may shortly need drug treatment. Conversely, such an approach may also be used to retard drug treatment in low-risk patients with mild hypertension.

The present study also confirms the results of a smaller sample of the HARVEST study, which showed that the 825T allele is associated with increased LVMI. Furthermore, with regard to insulin resistance, our results extend previous reports that found an association between the T allele and reduced insulin sensitivity in hypertensive patients. In fact, at enrollment, patients with the T allele had higher fasting glucose and lower HDL cholesterol, even if within the normal range. As for the low creatinine levels in patients with the T allele, it must be noted that renal blood and/or plasma flow are normal to enhanced in borderline hypertension and that the 825T allele of the G-protein β3-subunit is associated with increased renal plasma flow, and the low creatinine levels may reflect such a renal hemodynamic pattern.

On the contrary, at variance with previous reports, in this selected cohort we did not find any relation between GNB3 genotypes and BMI. It must be underlined that in the HARVEST study, subjects at high cardiovascular risk, including obese subjects, were excluded. With such a preselected narrow range of BMI values, lack of association with a given genotype is not surprising.

Perspectives

In conclusion, we propose that the GNB3 825T allele may be regarded as a potential genetic marker for better defining the risk profile of never-treated hypertensive patients. Further studies are needed to precisely define the biochemical mechanisms by which enhanced G-protein signaling may contribute to the development of hypertension. This approach can improve the diagnosis and treatment of hypertensive patients.

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