Association between a polymorphism in the G protein β3 subunit gene (GNB3) with arterial hypertension but not with myocardial infarction


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Abstract

Objective: A polymorphism at position 825(C→T) of the G protein β3 (GNB3) gene was found to be associated with enhanced transmembrane signalling as well as with an increased prevalence of arterial hypertension. The aim of the present study was to further investigate the association of the GNB3 C825T allele status with arterial hypertension in a large population-based sample and its association with specific end organ damage, i.e. myocardial infarction (MI). Methods: Individuals from a population-based sample (n=2052) and patients suffering from premature MI (age at first MI ≤60 years, n=606) were studied by questionnaire as well as by physical examination and biochemical analyses. Results: In the population-based sample, the prevalence of arterial hypertension (blood pressure ≥160/95 mmHg and/or antihypertensive medication) was higher in individuals with the TT genotype (41.8%) as compared to heterozygote individuals (36.6%) or those with the CC genotype (32.75%) (P=0.02). This association was predominantly found in men. Moreover, men without antihypertensive medication carrying the TT genotype showed higher diastolic blood pressure than those carrying the CC genotype (86.5 vs. 83.7 mmHg, P=0.04). However, the genotype distribution and the allele frequencies were similar in both, the population-based and the MI patient sample. Furthermore, neither the age at the time of MI nor the location of the MI were related to the genotype distribution. Similarly, gender and age stratified analyses did not show any association of the GNB3 genotype and MI. Conclusions: In male individuals from a large population-based sample, the T allele of the GNB3 polymorphism was associated with arterial hypertension. However, the effects of the GNB3 825T allele on blood pressure were small and did not translate to a clinically relevant increase of risk for MI. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Epidemiology; G-proteins; Gene expression; Hypertension; Infarction

1. Introduction

Heterotrimeric GTP-binding proteins (G proteins) are essential partners of multiple transmembrane receptors for the activation or inhibition of intracellular signalling cascades. Specifically, most vasoactive or growth stimulating factors communicate via G proteins in virtually all cardiovascular tissues. Recently, a polymorphism in the G protein β3 subunit gene (GNB3) exchanging cytosine to thymidine (C825T) has been discovered in selected patients with essential hypertension and considered as a candidate mutation for both, arterial hypertension and atherosclerosis [1]. The T allele of the GNB3 polymorphism was related to an RNA splice variant that results in the deletion of nucleotides 498–620 of exon 9 and

Abbreviations: MONICA, monitoring of trends and determinants in cardiovascular disease; GNB3, G protein β3 subunit gene; MI, myocardial infarction; LDL cholesterol, low density lipoprotein; HDL cholesterol, high density lipoprotein; PCR, polymerase chain reaction; BMI, body mass index

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structural changes in the β-subunit [2]. Moreover, an enhanced signal transduction via pertussis toxin-sensitive G proteins was observed in lymphoblast lines from hypertensive individuals carrying the T allele [2], which suggests that this genetic variation may indeed affect signal transduction. In recent studies, the association of the T allele of the GNB3 polymorphism with arterial hypertension has been confirmed in smaller cohorts [3–5]. However, some authors reported divergent results [6,7]. Based on the originally reported relative risk of arterial hypertension of 1.44 for individuals carrying the TT genotype [2], none of the previous studies was sufficiently powered to conclusively document a positive association with arterial hypertension.

The aim of the present study was, therefore, to investigate the association of the GNB3 C825T allele status with arterial hypertension in a large, sufficiently powered population-based sample (n=2052). Since arterial hypertension is an important risk factor for development of cardiovascular complications, such as myocardial infarction, a genetic variation causing arterial hypertension may also be an important candidate gene for myocardial infarction. Thus, the second aim of this work was to examine the association of the GNB3 C825T polymorphism with myocardial infarction in 606 affected patients.

2. Methods

2.1. Population-based sample

A large population-based sample (n=2052) was examined at the occasion of the echocardiographic substudies of the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) surveys in Augsburg, Germany, in 1994 (n=675) and in 1995 (n=1675). The population was studied by physical examination, blood testing, and a standardised interview including socio-economic background, history and actual presence of coronary risk factors (such as arterial hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking) as well as medication. All tests were taken by specially trained personnel in a study centre that provided a relaxed atmosphere. Blood pressure was taken according to MONICA guidelines using the random zero method and standard mercury sphygmomanometers [8,9]. Body weight and height were determined and body mass index was calculated as weight divided by the square of height. Blood was drawn for biochemical analyses from all patients in lying position. Serum tubes were centrifuged immediately and sent to the Clinical Chemistry Laboratory of the Central Hospital Augsburg for measurement of glucose, glycosylated haemoglobin (HbA1c), total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. LDL cholesterol levels were determined using the Friedewald formula when triglycerides were below 400 mg/dl (4.52 mmol/l). Data on 608 of these individuals have been reported previously [5].

2.2. Myocardial infarction patients

Patients suffering from premature myocardial infarction (MI; first MI prior to the age of 60 years) were identified through the Augsburg MONICA MI register. Starting in 1984, this register has collected information on all patients suffering from MI in the urban and surrounding rural areas of Augsburg. The diagnosis of MI was established according to the MONICA diagnostic criteria [8]. In June 1996, a total of 1187 patients being alive and having suffered from premature MI were registered. Between 1996 and 1997, all individuals with living siblings were contacted and, with informed consent, invited to participate in the study. A total of 606 MI patients (529 male, 77 female) were studied according to a similar protocol as described above. The investigation conforms with the principles outlined in the Declaration of Helsinki [10].

2.3. Arterial hypertension

For this study, arterial hypertension was defined for MI patients and normal population as blood pressure ≥160/95 mmHg or regular intake of antihypertensive medication. Antihypertensive medication was defined as the intake of drugs known to lower blood pressure, such as diuretics, β-blockers, vasodilators, ACE inhibitors, α-blockers, calcium channel-blockers.

2.4. G protein β3-subunit polymorphism

DNA was extracted from whole blood drawn from all individuals and the GNB3 genotype was determined according to the protocols described previously [2,5]. Briefly, PCR reactions were performed with the primers 5’-TGACCCACTTGCCACCCGTGC-3’ (sense) and 5’-GCAGCAGCCAGGGCTGGC-3’ (antisense) and amplified with denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 1 min, annealing at 64°C for 1 min and extension at 72°C for 1 min and a final extension at 72°C for 7 min. A second amplification was carried out for optimising the results. For this step, the products were denatured for 5 min at 95°C and amplified by 35 cycles of denaturation at 95°C for 1 min, annealing at 63°C for 30 s and extension at 72°C for 30 s and a final extension at 72°C for 7 min. As primers 5’-CTGCCCCCTAGTTCTTCC-3’ (sense) and 5’-CTGGCCCCTTACCCACAG-3’ (antisense) were used. PCR products were incubated with BseDI restriction enzyme (0.1 Unit at 60°C) (Promega, Germany) and
separated on a 2.5% agarose gel. The products were visualised by UV transillumination. The unrestricted PCR product corresponds to the T allele and has a size of 268 bp, whereas the restricted product corresponds to the C allele generating two bands sized 152 bp and 116 bp.

2.5. Statistical evaluation

For the comparison of non-parametric values the $\chi^2$ test was used, whereas the two-tailed Student’s $t$-test for unpaired and normally distributed samples or ANOVA for testing of parametric values were applied. In addition, multiple regression analysis was performed with the confounding variables detailed for every calculation. An error probability of $<0.05$ was regarded as statistically significant. Based on the known distribution of the GNB3 genotypes and an estimated relative risk for arterial hypertension of 1.5 [2], we calculated for the population-based MONICA sample a power of 0.99 and a least significant number of 348 probands to detect a significant influence of the GNB3 gene on mild arterial hypertension (blood pressure $\geq 140/90$ mmHg or antihypertensive medication) ($\alpha$-value of 0.05). The least significant number is the minimal sample size to obtain significant results ($P<0.05$). Using the same parameters for moderate arterial hypertension (blood pressure $\geq 160/95$ mmHg or antihypertensive medication), the power was calculated to be 0.55 and the least significant number was 1,826. For the statistical evaluation of data including the power calculation, SPSS software version 9.0 for Windows was used.

2.6. Calculation of MI risk conferred by arterial hypertension in individuals with the GNB3 TT genotype

Previously, it could be shown that patients with mild arterial hypertension, i.e. blood pressure above 140/90 mmHg, carry a relative risk for the development of coronary heart disease of 1.67 [11]. According to this estimate we calculated the theoretical relative risk for MI the coronary heart disease of 1.67 [11]. According to this blood pressure, such as age, gender, body mass index, and arterial hypertension, i.e. blood pressure above 140 / 90 mmHg, carry a relative risk for the development of arterial hypertension, i.e. blood pressure above 140 / 90 mmHg, carry a relative risk for the development of Linear regression analysis including factors influencing arterial blood pressure (Table 2). These associations were more prominent in men. In women similar trends could be recognised (Fig. 1). Interestingly, when GNB3 genotype distribution was examined in groups classified as blood pressure of $>140/90$, $>160/95$, $>180/100$ or $>190/105$ mmHg, the TT genotype group was more frequent in men with very high blood pressure (Table 2). Specifically, in men with the TT genotype, the prevalence of a diastolic blood pressure of $\geq 105$ mmHg was significantly higher (14.4%) than in the CT (7.3%) and the CC genotype groups (4.9%) ($P<0.002$).

Linear regression analysis including factors influencing blood pressure, such as age, gender, body mass index, and the GNB3 polymorphism revealed for the GNB3 TT genotype as compared to the GNB3 CC genotype an increase of the relative risk for arterial hypertension of 1.51 (95% confidence interval (CI), 1.08–2.11) and for the

3. Results

3.1. Anthropometric data

Complete genotyping and phenotyping was available in a total of 2098 individuals from the population-based MONICA survey. From this sample, 46 individuals had suffered from myocardial infarction and were excluded from the association study with arterial hypertension. In the remainder of the sample (2052 individuals, 1020 males and 1032 females), the allele frequencies were distributed according to Hardy–Weinberg equilibrium. Anthropometric and biochemical characteristics are shown in Table 1.

3.2. Association of the GNB3 polymorphism with arterial hypertension

In the population-based MONICA sample, 733 probands (35.2%) presented with either a history of arterial hypertension or actual hypertension (blood pressure $\geq 160/95$ mmHg) and/or antihypertensive treatment. The prevalence of arterial hypertension was significantly higher in the TT genotype group as compared to the CC genotype group (41.8 vs. 32.5%, respectively; $P=0.018$; Fig. 1). This observation was in part related to an increased utilisation of antihypertensive medication in the TT genotype group (Table 2). These associations were more prominent in men. In women similar trends could be recognised (Fig. 1). Interestingly, when GNB3 genotype distribution was examined in groups classified as blood pressure of $>140/90$, $>160/95$, $>180/100$ or $>190/105$ mmHg, the TT genotype group was more frequent in men with very high blood pressure (Table 2). Specifically, in men with the TT genotype, the prevalence of a diastolic blood pressure of $\geq 105$ mmHg was significantly higher (14.4%) than in the CT (7.3%) and the CC genotype groups (4.9%) ($P<0.002$).

Linear regression analysis including factors influencing blood pressure, such as age, gender, body mass index, and the GNB3 polymorphism revealed for the GNB3 TT genotype as compared to the GNB3 CC genotype an increase of the relative risk for arterial hypertension of 1.51 (95% confidence interval (CI), 1.08–2.11) and for the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CC genotype (n=948)</th>
<th>CT genotype (n=893)</th>
<th>TT genotype (n=211)</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.5±0.4</td>
<td>53.8±0.4</td>
<td>55.0±0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.6±0.7</td>
<td>138.6±0.7</td>
<td>138.7±1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.1±0.4</td>
<td>83.8±0.4</td>
<td>84.1±0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.9±0.1</td>
<td>26.9±0.1</td>
<td>26.9±0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>235±1.7</td>
<td>234±1.8</td>
<td>232±3.4</td>
<td>0.8</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>144±1.7</td>
<td>145±1.7</td>
<td>143±3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54±0.7</td>
<td>53±0.6</td>
<td>55±1.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values are means±S.E.M. To convert cholesterol levels from mg/dl to mmol/l, multiply by 0.02586.
use of antihypertensive medication of 1.79 (95% CI, 1.21–2.66), respectively. Moreover, in male individuals without antihypertensive treatment, the GNB3 polymorphism was significantly related to diastolic blood pressure (β-coefficient 1.57, 95% CI, +0.26 to +2.89), but not to systolic blood pressure (β-coefficient 0.40, 95% CI, −1.62 to +2.42).

3.3. Association of the GNB3 polymorphism with myocardial infarction

The allele frequencies of the T allele of the GNB3 genotype were similar in the normal population sample and 606 patients with premature MI (31.3 and 33.5% in men and 32.8 and 27.2% in women, respectively, P=n.s.).
Likewise, the GNB3 CC, CT, and TT genotypes were found at similar frequencies in MI patients and in participants of the population-based survey with no previous MI, respectively (Table 3). Similar results were obtained after adjustment for potential confounding factors (age, gender, body mass index, systolic blood pressure, and antihypertensive drug treatment) (data not shown) and after stratification in subgroups defined by presence or absence of coronary risk factors (Table 4). Given the limitations of such case-control analysis, we examined whether the lack of difference in allele frequencies between the MI patients and the survey population might be explained by differences in the size or location of infarctions, or the age at the time of infarction, i.e. factors that might affect survival after infarction. However, the age at the time of MI, the time that had elapsed between the first MI and presentation at the study centre, and the localisation or size of the MI, i.e. factors that might affect survival after MI, were similarly distributed in the three genotype groups (Table 5).

### 3.4. Arterial hypertension related risk for MI in the TT genotype group

In order to resolve the discrepant findings with respect to a positive association with arterial hypertension and a negative association with MI, we calculated the risk of MI that can be attributed to an elevated prevalence of arterial hypertension in the GNB3 TT genotype group (see Methods). Given, firstly, that arterial hypertension increases the risk of MI by a factor of 1.67 [11], and secondly, that the risk to present with arterial hypertension with the TT genotype is increased by a factor of 1.51, the theoretical relative risk of MI in the GNB3 TT genotype group as compared to the CT and CC genotype group is 1.04. We next multiplied the proportion of the GNB3 TT genotype in the population-based sample (10.28%) with the theoretical risk increase related to arterial hypertension as calculated above (1.04). The number of individuals expected to carry the GNB3 TT genotype and to have suffered from MI was calculated to be 65. In fact, we counted 66 individuals with the GNB3 TT genotype in our sample of MI patients (n=606), or a relative risk of 1.05. Assuming this relative risk and that the effect of the GNB3 polymorphism is entirely mediated through hypertension,
Table 5
Anthropometric and demographic data of myocardial infarction patients according to the 825C/T polymorphism in the GNB3 gene

<table>
<thead>
<tr>
<th>Variable</th>
<th>CC genotype (n = 277)</th>
<th>CT genotype (n = 263)</th>
<th>TT genotype (n = 66)</th>
<th>P value (ANOVA or χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>84.8</td>
<td>89.4</td>
<td>89.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Age at MI (years)</td>
<td>50.7</td>
<td>50.7</td>
<td>50.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Transmural MI (%)</td>
<td>95.6</td>
<td>96.5</td>
<td>95.2</td>
<td>0.82</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>42.6</td>
<td>44.5</td>
<td>46.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Maximal CK (U/l)</td>
<td>772</td>
<td>748</td>
<td>839</td>
<td>0.69</td>
</tr>
<tr>
<td>Maximal CK-MB (U/l)</td>
<td>72</td>
<td>67</td>
<td>75</td>
<td>0.48</td>
</tr>
<tr>
<td>Age at examination (years)</td>
<td>56.3</td>
<td>56.4</td>
<td>56.1</td>
<td>0.94</td>
</tr>
<tr>
<td>Time after MI (years)</td>
<td>5.5</td>
<td>5.7</td>
<td>5.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.6</td>
<td>28.3</td>
<td>28.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.95</td>
<td>1.96</td>
<td>1.96</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart rate (min)</td>
<td>66</td>
<td>66</td>
<td>69</td>
<td>0.16</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132</td>
<td>132</td>
<td>132</td>
<td>0.93</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84</td>
<td>85</td>
<td>84</td>
<td>0.38</td>
</tr>
<tr>
<td>Antihypertensive medication (%)</td>
<td>84.1</td>
<td>81.4</td>
<td>81.8</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>14.8</td>
<td>18.6</td>
<td>16.7</td>
<td>0.49</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>225</td>
<td>225</td>
<td>220</td>
<td>0.64</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>133</td>
<td>133</td>
<td>133</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>46</td>
<td>48</td>
<td>45</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Values are expressed as means. CC and TT genotype represent homozygosity and CT genotype represents heterozygosity for the GNB3 polymorphism; CK, creatine kinase; CK-MB, creatine kinase, heart-specific isoenzyme; systolic and diastolic BP, systolic and diastolic blood pressure, respectively; antihypertensive medication, % of subjects on antihypertensive medication. To convert values for cholesterol to mmol/l, multiply by 0.02586. * Defined as history of diabetes mellitus, fasting blood glucose >160 mg/dl, HbA1c >6.5% or intake of antidiabetic medication.

103,368 individuals with and without MI need to be studied to document a significant difference between groups.

4. Discussion

In the present study we demonstrate a significant association of the C825T polymorphism of GNB3 with both, arterial hypertension and antihypertensive treatment in a large sample of middle European Caucasians. These results confirm the association of the C825T polymorphism of GNB3 with arterial hypertension in a large population-based sample which was previously reported only on smaller and selected populations [2,3,5,7,12]. In contrast, other authors observed no significant contribution of this polymorphism on blood pressure in 479 and 681 cases, respectively [3,6]. An explanation for this discrepancy may be that the effects of the GNB3 polymorphism on systolic and/or diastolic blood pressure levels are small and require large sample sizes to be detectable.

Interestingly, the present large sample of normal population reveals that the group of individuals subjected to antihypertensive medication as well as the group with very high blood pressure levels were characterised by an excess of TT genotype carriers. In another paper [12], 110 hypertensive individuals with two hypertensive parents and a rather young age of onset were examined and the T allele was also associated with arterial hypertension and higher blood pressure levels. It, thus, appears that the TT genotype specifically increases the risk for severe hypertension. These data may give rise to the hypothesis that the T allele, instead of homogeneously raising the blood pressure by a certain extent, may be without significant effect in a large proportion of the population, but associate with a substantial effect in a small subgroup. This may be of relevance if the mutation causing arterial hypertension is in linkage disequilibrium but not identical with the T allele. Alternatively, specific gene–gene or gene–environment interactions may precipitate arterial hypertension in carriers of the TT genotype. Further studies have to address these hypotheses.

Vascular alteration related to the risk of arterial hypertension may also affect the risk of MI (as hypertension itself increases the risk of MI). Thus, we examined a large group of patients suffering from premature MI (i.e. age at first MI under 60 years). When comparing the allele frequencies of the GNB3 polymorphism with those of the population-based sample, no significant difference could be found. This finding indicates the absence of any detectable association of the GNB3 polymorphism with MI. Similar data were reported previously in a mixed population of MI patients from different regions in Europe [6]. Since the frequency of the GNB3 T allele varies considerably in both, geographical and ethnic groups [13], the previous study on ethnically and geographically distinct groups may be difficult to interpret. In the present study, we examined cases and controls from exactly the same geographical region reducing the ascertainment error.
and confirmed the previously documented negative association.

A limitation of the present study, however, is that only survivors of MI were included. It might, thus, be speculated that the apparent lack of association results from poor prognosis occurring in patients with sudden or early death after MI. Although this limitation cannot be excluded in any patient collection sampled after MI, selection by survival is unlikely since there was no relation between allele status and age at MI, size or location of MI nor with the time that elapsed since MI and the examination for the present study.

The most likely explanation for the apparent discrepancy between a positive association with arterial hypertension and a negative association with MI is that the relatively modest changes in blood pressure in the infrequent GNB3 TT genotype do not translate to a clinically detectable increase in risk of MI. In fact, we calculated the risk of MI that arises from the higher prevalence of arterial hypertension in the TT genotype group to be 1.04. In good agreement with this theoretical estimate, we observed a relative risk of 1.05 that was not significantly different from 1.0 in the presently studied T individuals with or without MI. Indeed, based on such risk increment and the low prevalence of the TT genotype, a much larger study with a sample size of greater 100,000 individuals has to be examined to test this relationship.

In conclusion, in a large population-based sample we demonstrated the significant association of the GNB3 825T allele with elevated diastolic blood pressure, predominantly in men without antihypertensive medication, but not on other coronary risk factors. Furthermore, no association of the GNB3 polymorphism with MI could be found.

Acknowledgements

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Appendix. Calculation of MI risk conferred by arterial hypertension in individuals with the GNB3 TT genotype

Step 1

Numbers of individuals with and without the GNB3 TT genotype classified by presence or absence of arterial hypertension

<table>
<thead>
<tr>
<th></th>
<th>Arterial hypertension</th>
<th>No arterial hypertension</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNB3 TT genotype</td>
<td>88</td>
<td>123</td>
<td>211</td>
</tr>
<tr>
<td>GNB3 CT/CC genotype</td>
<td>635</td>
<td>1206</td>
<td>1841</td>
</tr>
</tbody>
</table>

In patients with mild arterial hypertension, i.e. blood pressure above 140/90 mmHg, the relative risk for the development of coronary heart disease was previously shown to be 1.67 [11]. To calculate the relative risk of an MI in individuals carrying the GNB3 TT genotype, the numbers of all individuals with arterial hypertension (GNB3 TT genotype, n=88; GNB3 CT/CC genotypes, n=635) were multiplied by 1.67 (GNB3 TT genotype, $x_1=147$; GNB3 CT/CC genotypes, $x_2=1060$) and the numbers of those individuals without arterial hypertension (GNB3 TT genotype, n=123; GNB3 CT/CC genotypes, n=1206) were multiplied by 1.0 (no risk increase; GNB3 TT genotype, $y_1=123$; GNB3 CT/CC genotypes, $y_2=1206$).

Step 2

For determination of the risk ratio for MI (RR$_{MI}$) the calculated products of individuals carrying the GNB3 TT genotype were added ($x_1 + y_1 = 270$) and were divided by the actual sum of individuals with or without arterial hypertension carrying the TT genotype ($n=211$):

$$RR_{MI} (TT \text{ genotype}) = 270 / 211 = 1.279$$

(1)

The same was done for those individuals carrying the CT/CC genotypes ($x_2 + y_2 = 2266$ and actual sum of individuals with the CT/CC genotypes $n=1841$):

$$RR_{MI} (CT/CC \text{ genotype}) = 2266 / 1841 = 1.230$$

(2)

Step 3

The relative risk of individuals carrying the GNB3 TT genotype to develop MI attributable to the phenotype arterial hypertension is calculated as:

$$RR_{MI} (TT \text{ genotype}) / RR_{MI} (CT/CC \text{ genotype}) = 1.04$$

(3)
References