Interaction between the C(−344)T polymorphism of CYP11B2 and age in the regulation of blood pressure and plasma aldosterone levels: cross-sectional and longitudinal findings of the Olivetti Prospective Heart Study

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Objective To study the interaction between the C(−344)T CYP11B2 polymorphism and known determinants (age, body mass and dietary sodium) of blood pressure and plasma aldosterone.


Setting Medical centre of the Olivetti factories.

Participants In 1995, the C(−344)T polymorphism was characterized in 811 untreated men. A subgroup of 280 participants already seen in 1980 was the object of longitudinal analysis.

Main outcome measures Blood pressure, demographic, anthropometric and biochemical variables (serum and urinary electrolytes and plasma aldosterone) and frequency of the C(−344)T polymorphism.

Results In the whole population, there was no difference among genotypes for any of the variables examined. However, multiple regression showed a significant interaction between age (but not body mass or sodium intake) and genotype with regard to systolic (P = 0.03) and diastolic (P = 0.02) pressure variability independently of covariates. Diastolic pressure increased linearly with age in carriers of the T allele (TT, P < 0.001 and TC, P = 0.005), but not in CC homozygotes (P = 0.848). In T carriers – but not in CC homozygotes – blood pressure and serum potassium increased and plasma aldosterone and serum sodium decreased across quintiles of age (P < 0.001 for all trends). In the longitudinal study, diastolic pressure increased significantly over time only in T carriers (TC+TT: +2.6 ± 0.6, versus CC: −0.4 ± 1.5 mmHg, P = 0.04).

Conclusion Inter-individual variation of blood pressure and plasma aldosterone is affected by the interaction of CYP11B2 C(−344)T polymorphism and ageing, thus supporting a role for this variant in mechanisms affecting blood pressure regulation. J Hypertens 20:1785–1792 © 2002 Lippincott Williams & Wilkins.

Keywords: CYP11B2, aldosterone synthase, polymorphism, blood pressure, ageing, aldosterone

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Introduction

The role of genes regulating the components of the renin–angiotensin system and/or the factors involved in aldosterone production as a possible candidate for arterial hypertension has been studied extensively [1,2]. In particular, the candidacy for the CYP11B2 (aldosterone synthase gene) is based not only on its functional relevance for the synthesis of aldosterone but also on its pathogenic role in the syndrome of glucocorticoid-remediable aldosteronism [3], a rare form of inherited hypertension. Therefore targeted investigations have been conducted to explore the contribution of other variants of this gene to susceptibility for essential hypertension.

Among the frequent polymorphisms described for the CYP11B2 gene, the C(−344)T polymorphism in its transcriptional regulatory region has been reported to
be associated with hypertension [4–7] or with intermediate phenotypic indicators of aldosterone secretion [6–9]. However, the results of these studies have been controversial [10,11] and firm conclusions on the possible role of this variant on blood pressure and other related phenotypic variables have not been reached. Explanations for the inconsistencies are not obvious. Most of the studies carried out so far have been case–control studies involving selected hypertensive patients and their normal counterparts [4–7]. Most of them included patients on antihypertensive medications known to possibly affect both blood pressure and aldosterone levels, thus limiting their phenotypic characterization. Another reason for the inconsistency among various reports is that the phenotypic expression of a given susceptibility genotype may be confounded by the concomitant influence of environmental and personal factors (e.g. age, gender and race) with known and measurable effects on the inter-individual variance of the parameter under investigation. In particular, both blood pressure and aldosterone secretion regulation are influenced by factors such as age [12,13], body mass [14,15] and dietary sodium intake [16,17]. Previous studies suggested that the effects of CYP11B2 C(−344)T polymorphism on circadian variation of blood pressure [18] and other cardiovascular phenotypes, such as left ventricular mass [11,19] and baroreflex sensitivity [20], could be age-dependent.

The aim of the present study was to investigate the association of the CYP11B2 C(−344)T polymorphism with blood pressure, plasma aldosterone and other parameters of electrolyte homeostasis and to evaluate the interactions of this polymorphism with known demographic, anthropometric and environmental determinants (age, body mass and dietary sodium intake) of these phenotypic variables in a large sample of untreated workers attending the 1994–95 examination of the Olivetti Prospective Heart Study.

Methods

Population and field procedures

The study was performed at the Olivetti factories in Pozzuoli (Naples) and Marcianise (Caserta) and was part of a longitudinal investigation on the prevalence of cardiovascular risk factors in southern Italy involving the participation of the Olivetti factory male workforce. The methodology of the study has been described in detail elsewhere [21,22]. The study protocol was approved by the local Ethics Committee and participants gave their informed consent to participate.

Between May 1994 and December 1995, 1075 men in the age range 25–75 years were examined. The C(−344)T CYP11B2 polymorphism was characterized in 998 participants. After the exclusion of 187 men on antihypertensive drug treatment, a complete data set was available for 811 men who were included in the present analysis. A subgroup of the untreated subjects (n = 280) had already been seen in 1980 and was the object of the follow-up analysis.

The examinations were performed in the morning, in a quiet and comfortable room within the medical centre of the Pozzuoli and Marcianise factories: the study included a physical examination, anthropometric measurements, a resting 12-lead electrocardiogram, a blood test and a fasting timed urine collection. A fixed-sequence questionnaire was administered, and included demographic information and past medical history. A self-administered semiquantitative food frequency questionnaire was used for the assessment of dietary habits.

Blood pressure and anthropometric measurements

Blood pressure was measured between 0800 h and 1100 h, after the subject had been sitting upright for at least 10 min. Systolic and diastolic (phase V) blood pressure measurements were taken three times, 2 min apart, with a random zero sphygmomanometer (Gelman Hawksley Ltd, Sussex, England). The first reading was discarded and the average of the second two readings was recorded for systolic and diastolic blood pressure.

Body weight and height were measured on a standard beam balance scale with an attached ruler. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest centimetre, with subjects wearing only light indoor clothing without shoes. The body mass index was calculated as weight in kilograms divided by the square of their height in metres.

Both anthropometric and blood pressure measurements were performed by trained observers who had attended training sessions for standardization of the procedures. The operator code was recorded in order to check for possible measurement biases.

Fasting urinary collection, blood sampling and biochemical assays

On the morning of the study, after voiding and discarding overnight urine and drinking 400 ml of tap water, participants produced a fasting timed urine collection. The collection time and volume were recorded and a specimen was used for the analysis. At the mid-point of the urine collection and after the blood pressure measurements, a blood sample was obtained by venepuncture, with the subject in the seated position and without stasis, between 0800 and 1100 h. Biochemical determinations on serum and urine samples were performed as described below.

Blood specimens were immediately centrifuged and stored at −70°C until analysed. Creatinine was meas-
ured by the picric acid colorimetric method, serum and urinary electrolytes by atomic absorption spectrophotometry. Plasma aldosterone was measured by radioimmunoassay (DRG Instruments, GmbH-Germany) on 673 participants for whom a plasma sample was available. No difference in age, blood pressure and body mass was found between this group and the remaining study participants.

Creatinine clearance was calculated, corrected for body surface area when appropriate, and used as an index of glomerular filtration rate. Urinary sodium and potassium excretion rates on morning timed urine collection were calculated and taken as a surrogate index of dietary intake.

C(−344)T CYP11B2 gene polymorphism
Genomic DNA was isolated from leucocytes with a non-enzymatic, salting out procedure [23]. Segments of CYP11B2 were amplified from each DNA sample by the polymerase chain reaction (PCR) in 20 μl reactions containing 0.03 U Taq DNA polymerase, 1× concentration of the buffer supplied, 0.2 mmol/l concentration of each deoxynucleotide triphosphate, and 10 pmol of each primer. PCR conditions were: initial denaturation at 94°C for 5 min; then 35 cycles at 94°C for 1 min, at 67°C (annealing) for 1 min, and at 72°C (extension) for 2 min.

Subjects were genotyped for the −344 promoter polymorphism using primers CAGGAGGAGACCCCAT GTGAC (sense) and CCTCCACCCTGTTCAGCCC (antisense). Restriction fragment length polymorphism analysis (RFLP) was performed by adding 10 U of restriction endonuclease Hae III (Gibco-Invitrogen, Carlsbad, California, USA) in the appropriate buffer to 5 μl from each reaction (a 537 bp product) and by incubating at 37°C for 2 h [19]. The samples digested then underwent electrophoresis on 2.5% agarose gel with a Gel Electrophoresis Apparatus GNA-200 (Pharmacia Biotech, Milan, Italy), ethidium bromide stained, and analysed under UV light. Since the (−344)T allele lacks an HaeIII site (GGCC) present in the (−344)C allele, the (−344)T alleles are detected as fragments of 273 bp and (−344)C alleles as fragments of 202 bp (plus smaller fragments in each case).

A 10% random sample of the study population was double genotyped in a blinded fashion with concordant results.

Statistical analysis
Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-8.0, Chicago, Illinois, USA). As plasma aldosterone and serum electrolyte values did not follow a Gaussian distribution, log-transformation was executed and the log-transformed values were used for the analyses. One-way analysis of variance was used to evaluate differences between group means. Linear regression models were calculated: (1) to assess whether variation in CYP11B2 genotype made a statistically significant contribution to systolic and diastolic pressure variability allowing for the concomitant effects of known determinants of blood pressure variability such as age, body mass index and dietary sodium intake; (2) to evaluate whether the interaction between genotype and each of the above-mentioned factors affected blood pressure variability. The genotype effect was tested by entering in the equations the number of −344T alleles in the CYP11B2 (0, 1 and 2, corresponding to CC, TC and TT genotypes) as explanatory factor. The interaction between genotype and known explanatory factors of blood pressure variability was evaluated by including in the equation the ‘age × genotype’, ‘body mass × genotype’ and ‘dietary sodium intake × genotype’ product terms, respectively. The associations found in multivariate analysis were reported as multiple regression coefficients (b) and 95% confidence interval (CI). Simple linear correlation and regression analyses were used to test the bivariate associations between different variables in the whole population and among CYP11B2 genotypes. To analyse the effect of age on selected dependent variables in relation to the C(−344)T polymorphism, the population sample was divided into quintiles of age. The presence of a linear trend in mean values of the variables considered was tested across the quintiles of age in relation to the genetic background. Results are expressed as means and SDs or 95% CI, as indicated. Two-sided P values below 0.05 were considered statistically significant.

Results
C(−344)T CYP11B2 genotyping
Eight-hundred and eleven participants were included in the analysis [age 51.2 ± 7.4 years, body mass index (BMI) 26.7 ± 2.9 kg/m², systolic blood pressure 127.3 ± 15.7 mmHg, diastolic blood pressure 82.7 ± 9.2 mmHg (mean ± SD)]. Genotype frequency did not deviate from the Hardy–Weinberg equilibrium. The CC genotype was present in 182 individuals (22.4%), the TC genotype in 417 individuals (51.4%) and the TT genotype in 212 (26.2%). The frequency of the T allele (0.52) was similar to that described in previous studies on Caucasian populations [4,6,10].

Association of phenotypic variables with C(−344)T CYP11B2 genotypes
A comparison of selected variables in relation to C(−344)T CYP11B2 genotypes is shown in Table 1. No significant difference was detected in any of the variables investigated, including dietary sodium and potassium as measured by food frequency question-
naries and urinary excretion rates of sodium and potassium, taken as surrogate measures of intake.

Analysis of the interactions between C(−344)T CYP11B2 genotypes and determinants of blood pressure variability

The possible effect of C(−344)T CYP11B2 polymorphism on inter-individual blood pressure variance was explored by multiple regression analysis, allowing for the concomitant effect of known explanatory factors (such as age, body mass index and indicators of dietary sodium intake). As shown in Table 2, panel A, variation in CYP11B2 genotype did not make a statistically significant contribution to prediction of blood pressure, body mass and age being the sole significant determinants for both systolic and diastolic pressure. However, when the product term ‘age × CYP11B2 genotype’ was added in the equation, most of the independent effect of age on BP variability appeared to be explained by the statistically significant interaction between age and genotype (Table 2, panel B). Conversely, blood pressure variability was not significantly affected by the inclusion in the regression equation of the product terms ‘body mass × CYP11B2 genotype’ or ‘sodium intake × CYP11B2 genotype’ (as measured by food frequency questionnaires or by urinary excretion rate), respectively (equations not shown).

We thus conducted additional analyses to evaluate whether the relationships between blood pressure and age did vary among CYP11B2 genotypes. As expected, in the whole population both systolic ($r = 0.292, P < 0.001$) and diastolic ($r = 0.126, P < 0.001$) blood pressure were significantly and positively associated with age. However, separate analyses indicated genotype-dependent different trends for carriers of the T allele and CC homozygotes (Fig. 1). In subjects carrying the T allele (TC and TT genotypes), age was significantly and positively associated with both systolic and diastolic blood pressure; the strength of the association appeared to increase with the number of T allele copies. By contrast, CC homozygotes presented no association between diastolic blood pressure and age.

### Table 1 Characteristics of the population ($n = 811$) according to CYP11B2 C(−344)T genotypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>TT ($n = 212$)</th>
<th>TC ($n = 417$)</th>
<th>CC ($n = 182$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.5 ± 7.5</td>
<td>51.4 ± 7.1</td>
<td>50.3 ± 7.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 2.9</td>
<td>26.8 ± 2.8</td>
<td>26.6 ± 3.1</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127.5 ± 16.7</td>
<td>127.0 ± 15.1</td>
<td>127.7 ± 15.7</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82.6 ± 9.6</td>
<td>82.8 ± 8.9</td>
<td>82.4 ± 9.5</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per m²)</td>
<td>50.7 ± 13.7</td>
<td>49.8 ± 13.5</td>
<td>49.1 ± 12.2</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/l)</td>
<td>277.5 ± 166.9</td>
<td>277.0 ± 167.3</td>
<td>294.9 ± 192.2</td>
</tr>
<tr>
<td>Serum Na⁺ (mmol/l)</td>
<td>139.3 ± 2.0</td>
<td>139.3 ± 2.1</td>
<td>138.9 ± 2.2</td>
</tr>
<tr>
<td>Serum K⁺ (mmol/l)</td>
<td>4.8 ± 0.4</td>
<td>4.8 ± 0.4</td>
<td>4.8 ± 0.4</td>
</tr>
<tr>
<td>Dietary Na⁺ (mg/1000 kcal)</td>
<td>1036.8 ± 252.1</td>
<td>1054.2 ± 261.2</td>
<td>1036.9 ± 254.2</td>
</tr>
<tr>
<td>Dietary K⁺ (mg/1000 kcal)</td>
<td>1606.5 ± 325.5</td>
<td>1600.4 ± 334.2</td>
<td>1575.9 ± 299.5</td>
</tr>
<tr>
<td>U-Na⁺ rate (µmol/min)</td>
<td>156.4 ± 85.4</td>
<td>149.2 ± 76.5</td>
<td>142.9 ± 71.5</td>
</tr>
<tr>
<td>U-K⁺ rate (µmol/min)</td>
<td>57.8 ± 26.7</td>
<td>55.1 ± 28.0</td>
<td>52.6 ± 24.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. BMI, body mass index. aData available for $n = 673$ (CC = 152; TC = 350; TT = 171). bUrinary sodium excretion rate. cUrinary potassium excretion rate.

### Table 2 Stepwise multivariate regression equations, systolic and diastolic blood pressure as dependent variables

<table>
<thead>
<tr>
<th>Explanatory factor</th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Panel A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.817 (0.468, 1.166)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.689 (0.450, 0.728)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>U-Na⁺ rate (µmol/min)</td>
<td>0.004 (−0.009, 0.017)</td>
<td>0.333</td>
</tr>
<tr>
<td>CYP11B2 genotypeab</td>
<td>−0.632 (−2.1, 0.8)</td>
<td>0.399</td>
</tr>
<tr>
<td>Panel B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.819 (0.471, 1.167)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.163 (−0.046, 0.357)</td>
<td>0.434</td>
</tr>
<tr>
<td>U-Na⁺ rate (µmol/min)</td>
<td>0.004 (−0.009, 0.017)</td>
<td>0.537</td>
</tr>
<tr>
<td>CYP11B2 genotypeab</td>
<td>−11.4 (−21.2, −1.6)</td>
<td>0.023</td>
</tr>
<tr>
<td>‘Age × CYP11B2 genotype’</td>
<td>0.212 (0.021, 0.402)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Multiple regression coefficients (B) and 95% confidence interval (CI) of B are given for the effects of the factors selected into each model. aUrinary sodium excretion rate. bUrinary potassium excretion rate.
and the association between age and systolic blood pressure was weaker, albeit still statistically significant.

The regression slope of diastolic blood pressure on age was not significantly different from zero in the CC group. Statistically significant differences were found by comparing CC with both TC (mean difference between slopes 0.213 mmHg/year, 95% CI of the difference 0.001–0.427, \( P = 0.05 \)) and TT subjects (mean difference between slopes 0.264 mmHg/year, 95% CI of the difference 0.01–0.513, \( P = 0.03 \)).

**Genotype-dependent relationships between phenotypic variables and age**

Given the different behaviour observed in T carriers and C homozygotes, the population was divided into two groups: subjects with T allele (TC+TT group) and subjects without (CC group). The sample was thus stratified by quintiles of age, and the presence of a linear trend in mean values of phenotypic variables, such as blood pressure, plasma aldosterone and serum electrolytes, was tested across the quintiles of age in the two groups (Table 3, A–B). In the T carriers, a graded and statistically significant increase in both systolic and diastolic blood pressure was observed across quintiles of age. In this group, a statistically significant age-related trend to a decrease in plasma aldosterone and serum sodium levels and to an increase in serum potassium level was also observed (Table 3, A). In contrast, no similar trends were observed in the CC group, apart from the increase in systolic blood pressure across quintiles of age (Table 3, B).

**Follow-up study**

A subgroup of the study population (\( n = 280 \)) had been already seen in 1980: 21.9% of these had a CC genotype, 50.8% a TC genotype and 27.3% a TT genotype, a distribution similar to that found in the entire population. At baseline, the two groups (TC+TT and CC) were comparable for age, body mass index and systolic and diastolic blood pressure. Time changes in blood pressure over the 15-year interval between 1980 and the final examination were evaluated according to the two groups previously defined (CC, \( n = 63 \) versus TC+TT, \( n = 217 \)). Systolic blood pressure changes over the 15-year follow-up were not significantly different between the two groups (TC+TT: +3.3 ± 1.0 mmHg versus CC: +2.7 ± 2.3 mmHg) while an increase in diastolic blood pressure was observed only in the T group (TC+TT: +2.6 ± 0.6 mmHg versus CC: −0.4 ± 1.5 mmHg, \( P = 0.04 \)).

**Discussion**

The present study is the first population study of the C(−344)T \( CYP11B2 \) polymorphism and blood pressure based on a large sample size and on both cross-sectional and longitudinal observation with long-term follow-up. Most previous studies were case–control studies of selected hypertensive patients and appropriate normotensive controls [4–7]. The analysis carried out on the whole study population did not show a significant association between the C(−344)T \( CYP11B2 \) polymorphism and blood pressure or with intermediate phenotypes such as plasma aldosterone and serum electrolyte levels. Data on the association between the C(−344)T \( CYP11B2 \) polymorphism and blood pressure
are discordant, with some case–control studies suggesting a positive association of the −344T allele with hypertension [4,6], some an association with the C allele [5] and others no association [10,11]. Data on the association with indicators of aldosterone secretion are also controversial: while some studies suggested an association between the T allele and higher plasma aldosterone levels [4,8] or higher urinary aldosterone excretion rate [6], respectively, other studies found an association with the C allele [9] or no association at all [11]. Interestingly, however, previous studies suggested that the effects of CYP11B2 C(−344)T polymorphism on other cardiovascular phenotypes, such as left ventricular mass [11,19] and baroreflex sensitivity [20], might be age-dependent, being more evident in younger rather than in older population samples.

Therefore, we evaluated the interaction of CYP11B2 C(−344)T polymorphism with age in relation to blood pressure and plasma aldosterone levels in the Olivetti Study population. This analysis showed that the C(−344)T CYP11B2 genotype affected the relationships of both blood pressure and plasma aldosterone with age to a statistically significant extent. At multiple regression analysis, an independent ‘age × genotype’ interaction was observed after adjustment for the concomitant effects of other known determinants of blood pressure variability, thus suggesting a genotype-specific impact of age on blood pressure. When the variation of blood pressure with age was estimated by means of separate linear regression analyses, a significant heterogeneity was observed among genotypes. In particular, CC subjects exhibited a different regression line of diastolic blood pressure on age as compared with T carriers, suggesting a possible regulatory activity of this polymorphism on age-related blood pressure increase. In addition, the trend analysis on cross-sectional data demonstrated that only subjects with the T allele showed a significant increase in diastolic blood pressure across quintiles of age, a finding confirmed by the results of the analysis of the 15-year follow-up study. Systolic blood pressure increased with age in all groups but to a lesser extent in subjects with the CC genotype. In the participants carrying the T allele, a significant and progressive decline of plasma aldosterone levels with age was also observed, and this was associated with a decreasing serum sodium and increasing serum potassium levels.

This pattern is consistent with the previously recognized associations between age, blood pressure and aldosterone secretion. In industrially developed societies, blood pressure levels and prevalence of hypertension tend to increase with age [12]. In our population, the positive correlation between diastolic blood pressure and age is detectable only in the T allele carriers, who represented approximately 75% of

To read the entire text, please refer to the original journal article.
the population. This finding is confirmed by the data of longitudinal analysis on a representative, though smaller, subsample of the cohort. The lower blood pressure increase with age observed in CC subjects is similar to that described for some primitive societies living in a low-sodium environment [24]. Since in our study no differences in salt intake emerged from genotype comparison, these findings suggest that habitual dietary sodium intake may not be the sole factor responsible for the differences in the blood pressure rise with age observed in different populations, a genetic influence also being apparent.

The reduction in aldosterone levels with age has been demonstrated in animal models [25] and humans [13,26]. Both impaired conversion of steroidogenic precursors to aldosterone in zona glomerulosa cells – although this finding is limited to an experimental study on ovariectomized rats [27] – and reduced adrenal responsiveness to angiotensin II [28] have been advocated as possible causes of this phenomenon. In our population, T allele carriers showed the ‘physiological’ decline of plasma aldosterone with age, accompanied by concomitant changes in serum electrolyte levels. In contrast, no such evidence was found in the CC homozygotes.

In summary, CC homozygosis characterized a subset of population in whom ageing is associated with little or no changes in phenotypic variables such as diastolic blood pressure and plasma aldosterone levels.

Although these results should be considered hypothesis-generating and should be confirmed by further analysis in independent samples, several considerations argue against the possibility that these findings are attributable to a type 1 error. First, the inter-individual variability of the parameters under consideration is large enough to allow for an accurate phenotypic characterization of the participants. Individuals on pharmacological treatment for hypertension were excluded from the analysis, thus limiting confounding by drug treatment. An attempt was also made to characterize the dietary intake of sodium and potassium. Although the value of surrogate indicators of dietary intake such as those used in our study is limited, the influence of these variables has not been considered at all in the studies so far published. Second, in a sample of 420 young normotensive subjects a trend to higher aldosterone levels was observed in CC subjects than in TC+TT subjects in long-term follow-up. Some limitations of the present work are inherent to the nature of the Olivetti study cohort, which comprised only white male participants and may thus not be regarded as representative of the general population. For these reasons, the results of this study can be only generalized to a comparable white male population. Finally, the measurement of plasma renin activity – not performed at time of the study – might have been useful to gain further insight into the possible mechanism of the phenomena observed.

There are so far few data on possible functional expressions of the C(−344)T polymorphism of the CYP11B2. CYP11B2 activity in the zona glomerulosa is controlled primarily by angiotensin II and potassium [29]. The C/T substitution occurs in the 5′-flanking region of the gene, within a putative binding site for the steroidogenic binding factor, SF-1: thus the variant could result in different transcription rates of the gene [30]. It might be speculated that the C(−344)T allele confers a lower sensitivity to age-modulated factors affecting gene transcription, thus blunting the decline of aldosterone secretion with age.

In conclusion, while our findings appear to exclude that the C(−344)T polymorphism of the CYP11B2 has a direct influence in ‘setting’ a basic level of blood pressure in our population, they support a role for this genetic variant in modulating factors affecting blood pressure variations around this set point, and suggest that environmental and individual backgrounds should be taken into account when evaluating the influence of genes on multifactorial diseases such as arterial hypertension.

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