No association of the CYP3A5*1 allele with blood pressure and left ventricular mass and geometry: the KORA/MONICA Augsburg echocardiographic substudy

Wolfgang LIEB†, Juliane BOLBRINKER‡, Angela DÖRING§, Hans-Werner HENSE∥, Jeanette ERDMANN*, Heribert SCHUNKERT* and Reinhold KREUTZ‡

*Medizinische Klinik 2, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany, †Institut für Humangenetik, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany, ‡Abteilung Klinische Pharmakologie, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Berlin, Germany, §GSF Forschungszentrum für Umwelt und Gesundheit, Institut für Epidemiologie, Neuherberg, Germany, and ∥Institut für Epidemiologie und Sozialmedizin, Universität Münster, Münster, Germany

ABSTRACT

A polymorphism in the cytochrome P450 3A CYP3A5 enzyme has been implicated in BP (blood pressure) control and arterial hypertension. Carriers of the CYP3A5*1 allele had high, whereas homozygous carriers of the CYP3A5*3 allele exhibit low, CYP3A5 expression in the kidney, where CYP3A5 represents the major CYP3A enzyme. The aim of the present study was to investigate the association of the CYP3A5*1 allele with BP, arterial hypertension, LVM [(left ventricular) mass] and LV geometry in a large Caucasian-population-based cohort. We compared BP, LVM and the prevalence of hypertension between carriers (CYP3A5*1/*1 and CYP3A5*1/*3 genotypes) and non-carriers (CYP3A5*3/*3 genotype) of the CYP3A5*1 allele in the echocardiographic substudy of the third MONICA (MONItoring trends and determinants in CArdiovascular disease) Augsburg survey. After exclusion of 269 individuals who were taking antihypertensive medication, 530 women and 554 men were available for analysis, revealing allele frequencies of 5.8 and 94.2% for the CYP3A5*1 and CYP3A5*3 alleles respectively. Overall, the presence of the CYP3A5*1 allele exhibited no effect on systolic or diastolic BP in either gender. One-third of the individuals in this cohort were hypertensive (BP ≥ 140/90 mmHg), and the genotype distribution between normotensive and hypertensive individuals revealed no association between CYP3A5*1 and hypertension after adjustment for age, BMI and gender (odds ratio, 1.02; P = 0.92). Moreover, no effect of CYP3A5*1 on LVM, thickness of the septal and posterior wall and LV end-diastolic diameter was found. We conclude that CYP3A5*1 allele exhibits no significant effect on BP, LVM and LV geometry in the KORA/MONICA echocardiographic substudy.

Key words: blood pressure, cytochrome P450 3A (CYP3A), echocardiography, hypertension, left ventricular mass, pharmacogenetics.

Abbreviations: BMI, body mass index; BP, blood pressure; BSA, body surface area; CI, confidence interval; CYP3A, cytochrome P450 3A; DBP, diastolic BP; GFR, glomerular filtration rate; eGFR, estimated GFR; KORA, Co-operative Health Research in the Augsburg Area; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVH, LV hypertrophy; LVM, LV mass; LVMi, LV mass index; MONICA, MONItoring trends and determinants in CArdiovascular disease; OR, odds ratio; PP, pulse pressure; PREVEND, Prevention of REnal and Vascular ENd stage Disease; PWT, posterior wall thickness; SBP, systolic BP; SWT, septal wall thickness.

Correspondence: Professor Reinhold Kreutz (email reinhold.kreutz@charite.de).

© 2006 The Biochemical Society
INTRODUCTION

Recently, a polymorphism in an isoenzyme of cytochrome P450 3A (CYP3A), CYP3A5, has attracted increasing attention in cardiovascular research. This results from the fact that CYP3A5 is not only involved in drug metabolism, but is also expressed in the human kidney, where it is the major CYP3A enzyme [1–3]. The renal expression of CYP3A5 in epithelial cells of the proximal tubule and collecting duct [4,5] represented the basis for its implication in BP (blood pressure) and volume control and, thus, the pathogenesis of arterial hypertension. One potential mechanism by which CYP3A5 could mediate BP effects results from the fact that CYP3A enzymes metabolize endogenous corticosteroids and mineralocorticoids in humans and animals to their 6β-hydroxylated metabolites [3,6–8]. In the kidney, this could lead to a decreased stimulation of the mineralocorticoid receptor and thus lower sodium re-absorption via the epithelial sodium channel [6,9].

Interestingly, the expression of CYP3A5 has a strong genetic basis and is linked to a single nucleotide polymorphism (A6986G) in intron 3 of CYP3A5, which disturbs the correct splicing of transcripts and leads to low expression and enzyme activity. Thus low expression of CYP3A5 is found in homozygous carriers of the CYP3A5*3 allele, whereas homozygous and heterozygous carriers of the CYP3A5*1 allele exhibit high expression of CYP3A5 [1,3,10,11]. Therefore the observed higher renal expression of CYP3A5 in carriers of CYP3A5*1 could affect BP regulation in these individuals.

Recent studies, however, have reported controversial results as to the role of CYP3A5*1 in BP regulation and its association with hypertension [1,12–15]. The aim of the present study therefore was to test further the role of CYP3A5*1 in a large population-based sample of Caucasian origin including both women and men in which, after exclusion of individuals taking antihypertensive medication, one-third (33.3%) of the individuals were hypertensive (BP ≥140/90 mmHg).

The functional effects of CYP3A5 in the cardiovascular system could be mediated by its effects on renal sodium re-absorption [6,9,16]. Sodium intake and salt-sensitive BP regulation are linked significantly to the cardiac structure, LVH [LV (left ventricular) hypertrophy] [17,18] and LV dysfunction [19]. Furthermore, LVH represents one of the most frequent and clinically important examples of hypertension-induced organ damage [20–22] and salt-sensitive hypertension contributes significantly to its development [19,23]. Therefore the effect of CYP3A5*1 on echocardiographically determined parameters of LVM (LV mass) and LV geometry was also evaluated in the present study.

METHODS

Study population

The subjects of this study participated in the echocardiographic substudy (total n = 1674) of the third MONICA (MONItoring of trends and determinants in CArdiovascular disease) Augsburg survey [24], which is now continued in the framework of KORA (Co-operative Health Research in the Augsburg Area). Individuals were all Caucasians and originated from a random gender- and age-stratified sample of all German residents from the Augsburg area. The third survey represents individuals from 25–74 years of age, and approx. 300 subjects are present for each 10-year increment. The population was studied by physical examination, blood testing and a standardized interview, including medical history, physical activity, medication and personal habits. Resting BP was taken according to MONICA guidelines using the random zero sphygmomanometer after subjects had been resting in a sitting position. Individuals on antihypertensive medication were excluded, and the mean of the second and third recordings was calculated and employed to define hypertension as a BP ≥140/90 mmHg. Body weight (in kg) and height (in m) were determined with subjects wearing light clothing.

Written informed consent was obtained from all subjects, and the local Ethics Committee approved the study protocol.

Echocardiographic measurements

Two-dimensional guided M-mode echocardiograms were obtained using Sonos 1500 (Hewlett Packard) by two expert sonographers. M-mode tracings were recorded on strip-chart paper at 50 mm/s. To reduce interobserver variability, all M-mode tracings were analysed by a single cardiologist, who was blinded to the clinical and biochemical data. Measurements for M-mode-guided calculation of LVM were taken just below the tip of the mitral valve. Only high-quality tracings that demonstrated optimal visualization of endocardial and epicardial surfaces throughout the cardiac cycle were used. This resulted in the exclusion of 16% of the potential subjects. LVEDD (LV end-diastolic diameter) and SWT and PWT (septal wall and posterior wall thickness respectively) were measured according to the recommendations of the American Society of Echocardiography [25]. LVM was calculated using the formula LVM (g) = 0.8 × 1.04 [(LVEDD + SWT + PWT)3 − LVEDD3] + 0.6, as described by Devereux et al. [26]. LVMi (LVM index) was indexed to BSA (body surface area; LVMi = LVM/BSA). LVH was defined as LVMi >134 g/m2 in men and >110 g/m2 in women [27].

Biochemical analyses

Blood was drawn for biochemical analyses from non-fasting subjects. Creatinine was assessed quantitatively...
with an enzymatic colorimetric test (Hitachi 717; Boehringer Mannheim). eGFR [estimated GFR (glomerular filtration rate)] was calculated using the modified MDRD (modification of diet in renal disease) equation [28]:
\[
eGFR (\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{m}^{-2}) = 186 \times (S_c)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{if female})
\]
where \(S_c\) is serum creatinine concentration (in mg/dl).

**Determination of the CYP3A5 genotype**

Genotyping was performed by real-time PCR as reported previously [29]. The ABI PRISM® 7000 SDS instrument, in conjunction with the ABI TaqMan Universal Master Mix (Applied Biosystem), was used to perform the assays [30]. Appropriate primers and fluorogenic probes were designed with the Primer Express® software. Fluorogenic probes were synthesized by TIB Molbiol, and primers were obtained from Proligo. Primers were selected according to the sequence available at GenBank® (accession number NG_000004) [31]. The following probes and primers were used for genetic determination of the CYP3A5*1 and CYP3A5*3 alleles (nt 260167G > A): the fluorogenic probes were VIC®-5′-TGCTTTCAGTATCTCTT (18-mer, nt 260158–260175) and FAM-5′- TGCTTTCAGTATCTCTTC (19-mer, nt 260158–260176; where FAM is 6-carboxyfluorescein), and the primers were ACCCAGCTTAAGAATGCTCTCTACT (forward; 24-mer, nt 260098–260121) and GAAGGTAATGTGCTTCCAAACAG (reverse; 23-mer, nt 260178–260200). TaqMan assays were performed in 384-well plates prepared with the GENESIS Freedom pipetting robot from TECAN. Using this methodology, a total of 1359 individuals were genotyped successfully.

**Statistical analyses**

To determine whether the genotypes deviated from the Hardy–Weinberg equilibrium, actual and predicted genotype counts were compared by a \(\chi^2\) goodness-of-fit test with one degree of freedom. Least-square means for SBP and DBP (systolic and diastolic BP respectively) as well as for PP (pulse pressure; defined as SBP − DBP) were calculated for all genotype groups. Due to the expected small number of individuals homozygous for the CYP3A5*1 allele and according to the expectation that CYP3A5*1 allele carriers have a higher CYP3A5 enzyme activity [1,10,11], CYP3A5*1/*1 individuals and CYP3A5*1/*3 individuals were analysed as a combined group compared with the CYP3A5*3/*3 homozygotes with low expression [29]. Thus the influence of the presence or absence of the CYP3A5*1 allele in a dominant model was analysed primarily and descriptive \(P\) values of a two-tailed Student’s \(t\) test for independent groups are reported. All analyses were performed for the entire population and stratified by gender. A logistic regression model with hypertension (presence compared with absence of hypertension) as the dependent variable and genotype, age, gender and BMI as the explanatory variables was developed. ORs (odds ratios), 95 % CIs (confidence intervals) and two-tailed descriptive \(P\) values of the WALD \(\chi^2\) test are reported for the entire population and for males and females separately. Echocardiographical data and eGFR measurements according to CYP3A5 genotypes were compared descriptively using multiple linear regression. Echocardiographical data were adjusted for age, BMI, SBP and gender. Furthermore, eGFR according to CYP3A5 was considered by calculating least-square means adjusted for age, gender and diabetes. In addition, adjusted mean differences between carriers and non-carriers of the CYP3A5*1 allele with corresponding 95 % CIs were calculated for SBP, DBP, LVM and eGFR. All calculations were performed using SPSS version 12.1. All \(P\) values should be considered descriptive.

**RESULTS**

In total, 670 women and 689 men were genotyped successfully. Six individuals were excluded because of missing covariates. Furthermore, 269 individuals taking antihypertensive medication (131 men and 138 women) were excluded, leaving 530 women and 554 men for the final analyses. The allele frequencies of the CYP3A5*1 and CYP3A5*3 allele were 5.8 and 94.2 % respectively. The CYP3A5*1/*1, CYP3A5*1/*3 and CYP3A5*3/*3 genotypes were found in 0.5, 10.6 and 88.9 % of the population. These frequencies do not deviate from those predicted by the Hardy–Weinberg equilibrium and were similar to those reported previously in Caucasians [9].

Table 1 displays the baseline characteristics, BP levels, LVM measurements and eGFR measurements according to CYP3A5 genotype in the overall study population and when stratified by gender. Carriers of the CYP3A5*1 allele were slightly younger than non-carriers, whereas no differences in BMI and the prevalence of diabetes were found in men and women between carriers and non-carriers of the CYP3A5*1 allele.

**Association of CYP3A5*1 with BP and hypertension**

In the overall analysis, the presence of the CYP3A5*1 allele exhibited no effect on SBP, DBP or PP in either men or women (Table 1). The observed adjusted difference between CYP3A5*1/*1 + CYP3A5*3/*1 individuals compared with CYP3A5*3/*3 individuals was −0.40 (95 % CI, −3.45 to +2.65) mmHg for SBP and 0.31 (95 % CI, −1.67 to +2.30) mmHg for DBP. Overall, 361 (33.3 %) individuals were diagnosed with hypertension.
Table 1. Baseline Characteristics, and BP, LVM and eGFR measurements, according to the CYP3A5 genotype in the entire study population and when stratified by gender.

<table>
<thead>
<tr>
<th>CYP3A5 genotype</th>
<th>Combined</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.2 ± 3.3</td>
<td>49.5 ± 3.6</td>
<td>48.9 ± 3.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 3.8</td>
<td>24.7 ± 3.3</td>
<td>24.1 ± 3.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.7 ± 1.9</td>
<td>78.7 ± 2.1</td>
<td>81.4 ± 1.5</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134.8 ± 7.7</td>
<td>134.2 ± 7.2</td>
<td>134.3 ± 7.8</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>84.0 ± 1.8</td>
<td>85.7 ± 1.7</td>
<td>82.4 ± 1.7</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>50.1 ± 1.8</td>
<td>49.7 ± 1.5</td>
<td>51.9 ± 1.7</td>
</tr>
<tr>
<td>eGFR (ml·min⁻¹·1.73 m²)</td>
<td>107.2 ± 4.1</td>
<td>107.4 ± 4.2</td>
<td>107.0 ± 4.0</td>
</tr>
<tr>
<td>BP measurements†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP measurements‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI measurements§</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are adjusted for age, BMI and gender (combined group).

* P values from Student's t test for independent data for the analysis using a dominant model, i.e. comparing individuals with CYP3A5 */1− */1 and CYP3A5 */3− */3 individuals, are shown.
The baseline characteristics of the study population stratified by gender and hypertension status are shown in Table 2. The CYP3A5 genotype distribution in men and women with and without arterial hypertension is shown in Table 3. No association of the CYP3A5*1 allele with the prevalence of hypertension was found in our cohort in multivariate models adjusting for age, BMI and gender [OR, 1.02 (95% CI, 0.66–1.60); P = 0.92]. In normotensive females, a somewhat higher allele frequency for CYP3A5*1 was observed compared with the other groups (Table 3). However, no association between the presence of CYP3A5*1 and hypertension was detected in separate analysis in men [OR, 1.26 (95% CI, 0.69–2.32); P = 0.46] or women [OR, 0.85 (95% CI, 0.43–1.67); P = 0.63].

### Association of CYP3A5*1 with LV and LV geometry

LVM measurements were determined echocardiographically in 942 individuals (464 men and 478 women). No association of the CYP3A5*1 allele with LVMI, SWT, PWT or LVEDD was found by multivariate analyses in males and females in the combined analysis of both genders (Table 1). For LVMI, the observed adjusted difference between CYP3A5*1/*1 + CYP3A5*3/*1 individuals and CYP3A5*3/*3 individuals was −0.73 (95% CI, −3.81 to +2.34) g/m². The CYP3A5 genotype distribution was slightly different (P = 0.022) between individuals with (CYP3A5*3/*3, 93.8%); CYP3A5*3/*1, 3.1%; CYP3A5*1/*1, 3.1%) and without (CYP3A5*3/*3, 88.4%; CYP3A5*3/*1, 11.3%; CYP3A5*1/*1, 0.3%) LVH. However, in multivariate analyses, adjusting for age, BMI, SBP and gender, no relevant protective effect against LVH associated with the CYP3A5*1 allele was observed [OR, 0.66 (95% CI, 0.15–2.95); P = 0.59].

### Association of CYP3A5*1 with eGFR

We also analysed the association of CYP3A5*1 with renal function as determined by eGFR; however, no association in the entire population or in women was observed (Table 1). In the entire population, the observed adjusted difference assuming a dominant model for the rare CYP3A5*1 allele was 1.06 (95% CI, −3.02 to +5.13). In men, weak evidence for an association was found (P = 0.045). The genotype distribution was not different between individuals with mildly impaired renal function (eGFR < 90 ml·min⁻¹·1.73 m⁻²) and individuals with normal renal function (eGFR ≥ 90 ml·min⁻¹·1.73 m⁻²) either in the combined analysis of both genders or in separate analysis according to gender (results not shown).

### DISCUSSION

Research into the role of the CYP3A5 polymorphism in BP regulation was stimulated by an initial study in a small group of African–Americans in which higher BPs were reported in individuals carrying the CYP3A5*1 allele [1]. Subsequently, additional studies have analysed the role of CYP3A5 on BP in different populations and have produced controversial results [9,12–14,29]. In this regard, it is important to consider that the frequency of CYP3A5*1 carriers, i.e. high expressors of CYP3A5, shows extreme variations across human populations [3] and is significantly correlated with the distance from the equator, with the highest frequency of approx. 70% observed in Africans and the lowest, with approx. 10%, found in European Caucasians [16]. Consequently, the relevance of CYP3A5*1 may vary between different ethnic populations [3]. Owing to the relative low frequency in Caucasians, it appears particularly important...
to study large cohorts in this ethnic group. In the study by Ho et al. [12], no association between \( CYP3A5^*1 \) and hypertension was found in white patients from North America, whereas the proportion of salt-sensitive subjects was higher in white hypertensive \( CYP3A5^*1 \) carriers compared with non-carriers. In a population of elderly individuals (age ≥ 75 years) from Finland, Kivisto et al. [13] have shown that the proportion of individuals carrying the \( CYP3A5^*1 \) allele was significantly higher in hypertensives compared with normotensive elderly subjects, suggesting a role of \( CYP3A5^*1 \) in hypertension development in elderly Caucasian subjects.

More recently, Bochud et al. [15] analysed the effect of \( CYP3A5 \) polymorphisms on ambulatory BP and GFR in a cohort of 375 individuals recruited from families with at least two hypertensive siblings. The authors [15] reported an allele frequency of 43.7 % for \( CYP3A5^*1 \) compared with a frequency of 5.8 % in the Caucasian cohort of the present study. Although crude BP levels were similar between carriers and non-carriers of the \( CYP3A5^*1 \) allele in the study by Bochud et al. [15], the authors detected a significant positive interaction between \( CYP3A5^*1 \) and age for ambulatory SBP and DBP during the day, but not at night. They reported that \( CYP3A5^*1 \) carriers demonstrated a significant age-related BP increase. Interestingly, Bochud et al. [15] also investigated the effect of \( CYP3A5^*1 \) on renal sodium handling by fractional excretion of lithium and found that non-carriers of \( CYP3A5^*1 \) had decreased proximal tubular sodium re-absorption with age, whereas \( CYP3A5^*1 \) carriers did not. Further analysis between urinary sodium excretion, reflecting dietary salt intake, and ambulatory BP indicated that \( CYP3A5^*1 \) carriers tended to increase their night-time BP with increasing dietary salt intake more than non-carriers. The authors [15] suggested that carriers of \( CYP3A5^*1 \) appear to be more salt-sensitive than non-carriers, supporting a role of \( CYP3A5^*1 \) in salt-sensitive hypertension, which might be particularly important with increasing age [16,32].

In contrast, \( CYP3A5^*1 \) was found to be associated with lower SBP, but not DBP, in a homogenous group of 115 young white male students with normal or mildly elevated BPs [14]. This study was in agreement with our recent investigation [9] in a large population-based Caucasian cohort, i.e. PREVEND (Prevention of REnal and Vascular ENd stage Disease) study population, in which we also determined lower SBPs and PPs, but not DBPs, in carriers of the \( CYP3A5^*1 \) allele. Taken together, the latter two studies are in agreement with the postulated mechanism that renal \( CYP3A5 \) expression confers a BP-lowering effect by decreasing renal sodium re-absorption [9]. Nevertheless, these findings are at odds with the results obtained in the present study in which we found no association between \( CYP3A5^*1 \) and any BP phenotype in both men and women. This is of interest, as the subgroup analysis in the PREVEND population according to gender revealed that \( CYP3A5^*1 \) had a significant effect on SBP and PP only in females, but not in males [9].

Importantly, in the present analysis of the KORA/MONICA echocardiographic substudy population, no association of the \( CYP3A5^*1 \) allele with LVM measurements or LVH in multivariate models was detected. The finding of LV echocardiographic parameters is in line with the observation reported from Fromm et al. [14], who also performed echocardiographic analyses of LVM in their young male individuals and detected no effect of \( CYP3A5^*1 \) on cardiac parameters, although they did detect significantly lower SBPs in carriers of \( CYP3A5^*1 \).

In addition to effects on BP, Givens et al. [1] reported, in their small study in young healthy African-Americans, an association between \( CYP3A5^*1 \) and GFR measurements, i.e. creatinine clearance; this observation was only seen in females, but not in males, by comparing ten female \( CYP3A5^*1 \) carriers with five female non-carriers. This finding should be viewed with caution, as the numbers in the study [1] were clearly very small and a confounding factor due to differences in BMI in females could not be excluded, because values for creatinine clearance were not adjusted to BSA. In the more recent study by Bochud et al. [15], \( CYP3A5^*1 \) exhibited a significant effect on GFR measured by inulin clearance (\( P = 0.045 \)); however, the significance disappeared after the adjustment for BSA (\( P = 0.093 \)), and no significant association with creatinine clearance was observed. In contrast, Ho et al. [12] found no effect of \( CYP3A5^*1 \) on creatinine clearance and urinary albumin excretion in both African-Americans and Caucasians. Similarly, Fromm et al. [14] also found no effect of \( CYP3A5^*1 \) on GFR measurements in their carefully studied cohort of young Caucasian individuals. In this regard, a limitation of our present study arises from the fact that renal sodium handling was not studied and direct GFR measurements were not available. Nevertheless, determination of eGFR by the MDRD equation [28] revealed no overall significant effect of \( CYP3A5^*1 \), whereas only a subgroup analysis according to gender indicated higher GFR levels in male, but not female, carriers of \( CYP3A5^*1 \). Taken together, as evident from the controversial data reported so far, a consistent effect of \( CYP3A5^*1 \) on GFR is far from established.

Although the number of individuals (n = 1084) analysed in the present study from KORA/MONICA study population is still considerably higher and exceeds by far the number of Caucasians reported by others [1,13,14], it is still significantly lower compared with the 6777 individuals analysed in the PREVEND study [9]. Therefore the negative result in the present study may be, in part, related to a lack of statistical power. The observed adjusted difference between \( CYP3A5^*1/1 + CYP3A5^*3/1 \) individuals compared with \( CYP3A5^*3/3 \) individuals was -0.40 (95 % CI, -3.45 to +2.65) mmHg.
for SBP and 0.31 (95% CI, −1.67 to +2.30) mmHg for DBP. Thus, with a confidence of 95%, the true difference between the groups lies within this interval and a mean difference smaller than −3.45 or greater than 2.65 mmHg for SBP and smaller than −1.67 or greater than 2.30 mmHg for DBP can be excluded. For LVMII, differences smaller than −3.81 or greater than 2.34 g/m² between carriers and non-carriers of the CYP3A5*1 allele can be excluded with 95% confidence.

Another important issue relates to the higher frequency of individuals with hypertension (33.3%; defined as BP ≥140/90 mmHg) analysed in the present study from the KORA/MONICA study population compared with the PREVEND study population in which hypertension was less prevalent (22%). In this regard, it appears possible that the functional effect of CYP3A5*1 depends on the BP level and stage of hypertension and might be more relevant, in agreement with our recent analysis in the PREVEND study [9] and the study by Fromm et al. [14], at lower BP values. The biological effect at higher BP levels could be blunted or eliminated due to other genetic factors that come into play and/or compensatory mechanisms. The potential relevance of adaptive mechanisms has been highlighted in the recent study in young male individuals with normal or mildly elevated BPs [14]. In this study [14], the authors demonstrated that 96 individuals with the CYP3A5*3/*3 genotype had on average SBP values 5 mmHg higher compared with the nine carriers of the CYP3A5*1 allele, whereas serum aldosterone levels were significantly lower in CYP3A5*3/*3, suggesting a compensatory suppression of aldosterone in response to higher SBPs in these individuals [14]. Consequently, it appears of interest to pursue this hypothesis further and to perform both experimental and clinical studies on the role of CYP3A5 in BP control.

ACKNOWLEDGMENTS

This study was supported by grants from the Bundesministerium für Bildung und Forschung (to R. K.) and Nationales Genomforschungsnetz (Grant KGCV1, 01GS0416 to R. K.; and 01GS0418 to H. S. and J. E.).

REFERENCES