Association of the T8590C Polymorphism of *CYP4A11* With Hypertension in the MONICA Augsburg Echocardiographic Substudy

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Abstract—Genetic variants of the arachidonic acid monooxygenase *CYP4A11* result in decreased synthesis of 20-hydroxyeicostatetraenoic acid and experimental hypertension. Moreover, in humans, the T8590C polymorphism of *CYP4A11* displayed association with arterial hypertension. The aim of the present study was to further investigate this association in a large population-based sample. Therefore, the participants of the echocardiographic substudy of the third MONICA (MONitoring trends and determinants In CArdiovascular disease) survey (n=1397) were studied by standardized anthropometric, echocardiographic, and biochemical measurements as well as genotyping for *CYP4A11* T8590C allele status. Individuals with the CC genotype have higher systolic (CC 141.4±3.17 mm Hg versus CT 134.2±0.97 mm Hg and TT 134.3±0.53 mm Hg; $P=0.03$) and diastolic blood pressure levels (CC 85.4±2.06 mm Hg versus CT 80.3±0.63 mm Hg and TT 80.7±0.34 mm Hg; $P=0.02$). Accordingly, the odds ratio (adjusted for age, body mass index, and gender) of the CC genotype versus the CT and TT genotypes for hypertension was 3.31 (95% confidence interval [CI]), 1.38 to 7.96; $P=0.016$) in the entire study population, with similar trends in men (4.30 [95% CI, 1.08 to 17.15]) and women (2.93 [95% CI, 0.88 to 9.84]). Consistent with the renal effects of the gene, no blood pressure–independent association between the T8590C polymorphism and echocardiographic parameters of left ventricular function and geometry was found. In conclusion, our data strengthen the association between the T8590C polymorphism of *CYP4A11* and hypertension and suggest a recessive mode of inheritance. In contrast, we found no blood pressure–independent modulatory effect of *CYP4A11* T8590C on cardiac size, structure, and function. (***Hypertension*. 2005;46:766-771.)**

Key Words: genetics ■ polymorphism ■ hypertension, arterial ■ echocardiography

A variety of gene variants has shown association with arterial hypertension. However, only small or inconsistent effects on blood pressure were observed for most of the frequent polymorphisms of hypertension-related genes.[1] On the other hand, mutations with profound implications for blood pressure regulation were found predominantly in exceptional families.[2] Thus, despite extensive research, genetic testing for risk assessment in hypertension is not yet advisable for routine patient evaluation. A major challenge for this field will be the identification of genetic variants with reproducible and clinically as well as epidemiologically relevant effects on blood pressure regulation that, in addition, offer the potential of therapeutical intervention.

The *CYP4A* arachidonic acid monooxygenase oxidizes endogenous arachidonic acid to 20-hydroxyeicostatetraenoic acid (20-HETE). Depending on its expression at renovascular or tubular sites, the 20-HETE metabolite can act in a prohypertensive or antihypertensive manner.[3–6] Holla et al characterized a *CYP4A14* (−/−) knockout mouse as a model of gender-specific severe hypertension.[7] Evaluation of human homologues as potential novel genetic determinants in hypertension revealed 2 candidate genes: *CYP4A11* and *CYP4A22* from the *CYP4A* gene family.[8,9] Recently, *CYP4A11* but not *CYP4A22* was identified as the functional active protein that catalyzes the metabolism of arachidonic acid to 20-HETE in humans.[10] Screening for genetic variants revealed a cytosine for thymidine transition at nucleotide 8590 in exon 11, which results in a nonsynonymous phenylalanine to serine substitution at residue 434 of *CYP4A11*. The less frequent 8590C genotype, which corresponds to the 434S variant on protein

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level, affects the catalytic activity of the 20-HETE synthase through a loss-of-function mechanism.[10] This variant was associated weakly with hypertension in the Framingham Offspring Cohort. Similar results were obtained in white participants of the Tennessee Cohort. Subgroup analyses in these studies including blacks within the Tennessee Cohort did not show significant association, most likely because of insufficient power.[10]

This initial weak positive evaluation requires verification in an independent cohort to reduce the chance of being false-positive. Furthermore, the present analysis within the population-based MONICA (MONitoring trends and determinants In CArdiovascular disease) Augsburg echocardiographic substudy sample intends to evaluate the potential impact of the *CYP4A11* T8590C polymorphism on echocardiographic parameters of left ventricular (LV) function and geometry.

Methods

Study Population

The subjects of this study participated in the echocardiographic substudy (total n=1674) of the third MONICA Augsburg survey 1994/1995.[11–13] Subjects originated from a gender- and age-stratified random sample of all German residents of the Augsburg area. The third survey represents individuals 25 to 75 years of age and ≈300 subjects 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 blood pressure was taken according to MONICA guidelines using the random-zero method and standard mercury sphygmomanometers after subjects had been in a sitting position ≥30 minutes. Hypertension was defined as blood pressure ≥140/90 or the use of antihypertensive medications. Body weight in kilograms and height in meters were determined with subjects wearing light clothing. Written informed consent was obtained from all subjects, and a local ethical committee approved the study protocol.

Echocardiographic Measurements

A 2D guided M-mode echocardiogram recorded on a strip-chart paper at 50 mm/s was performed on each subject. LV end-diastolic (LVEDD) and LV end-systolic (LVESD) diameters, septal wall (interventricular septal [IVS]), and posterior wall dimension (PWD) thickness were measured according to the recommendations of the American Society of Echocardiography.[14] LV mass (LVM) was calculated using the formula: $LVM\ (g)=0.8\times1.04[(LVEDD+IVS+PWD)^3-LVEDD^3]+0.6$, as described by Devereux et al.[15] LVM was indexed to body surface area. LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) were calculated according to the Teichholz equations.[16] The ejection fraction (EF) was calculated as EF=LVEDV−LVESV/LVEDV.

Biochemical Analyses

Blood was drawn for biochemical analyses from nonfasting subjects. Creatinine was assessed quantitatively with an enzymatic colorimetric test (Hitachi 717; Boehringer Mannheim). Creatinine clearance was calculated using Cockcroft–Gault formula.[17]

Genotyping

Genotyping the T8590C polymorphism was performed using the 5′-exonuclease activity (TaqMan) assay on a HT7900 (Applied Biosystems). Single nucleotide polymorphism (SNP)-assay was ordered from Applied Biosystems through the Custom TaqMan SNP Genotyping Assays (forward primer: *CYP4*_434-F: 5′-GTGGCTGTGTTGAGCAGAAC-3′, reverse primer: *CYP4*_434-R: 5′-GTGCTCTCTCTGCAGGTGTTT-3′, probe 1: *CYP4*_434-VIC: 5′-AAAACGGAAAGGGTC-3′, probe 2: *CYP4*_434-FAM: 5′-AACGGGAAGGGTC-3′. With respect to sequence homology of 97% between *CYP4A11* and *CYP4A22*, primer and probe sequences guarantee *CYP4A11*-specific amplification. Probes were labeled with the fluorophore FAM or VIC. Genotyping was done on 384-well plates prepared with the GENESIS Freedom pipetting robot from TECAN. The universal polymerase chain reaction (PCR) Master Mix from Applied Biosystems was used in a 5-μL total reaction volume with 10 ng DNA per reaction. Allelic discrimination was measured automatically on the ABI Prism HT7900 (Applied Biosystems) using the Sequence Detection Systems 2.1 software (autocaller confidence level 95%). A total of 10% of all genotypes were repeated in independent PCRs to check for consistency and to ensure intraplate and interplate genotype quality control. No genotyping discrepancies were detected between the repeated samples. For the present study, 1397 individuals were successfully genotyped. The overall misgenotyping rate of 16% was attributable to insufficient PCR amplification because of inadequate DNA quality or quantity.

Statistical Analysis

To determine whether the genotypes of the *CYP4A11* T8590C polymorphism deviated from Hardy–Weinberg equilibrium, actual and predicted genotype counts were compared by a χ^2 goodness-of-fit test with 1 *df*.

Because it could not be excluded that the study sample deviates from a representative sample and that baseline factors are unequally distributed across genotypes, a multivariate model was chosen for the analysis.

To predict hypertension (presence versus absence of hypertension), a logistic regression model with genotype, age, gender, and body mass index (BMI) as explanatory variables was developed. All 2-way interactions between the genotype and covariates (age, gender, BMI) were considered and kept in the model if $P\leq0.05$. Based on the results by Gainer et al,[10] the genotype was coded for a dominant effect (CC+CT versus TT). As a second analysis, a recessive model (CC versus CT+TT) was considered. To adjust for the multiple testing of 2 genetic models, the *P* values for the genotypes were adjusted according to Bonferroni–Holm.[18] A 2-tailed adjusted *P* value of the WALD-χ^2 test ≤0.05 was considered significant. In addition, odds ratios (ORs) and 95% WALD confidence intervals (CIs) are reported for all explanatory variables. For description OR, 95% CI and 2-tailed *P* values of the WALD-χ^2 test are presented for males and females separately for both genetic models.

Least square means for systolic blood pressure (SBP) and diastolic blood pressure (DBP) adjusted for age, BMI, gender, and antihypertensive medication were calculated for all genotype groups. Furthermore, descriptive *P* values of a 2-tailed *t* test for independent groups for a dominant model (CC+CT versus TT) and a recessive model (CC versus CT+TT) are reported.

Echocardiographical data and blood pressure measurements according to 8590TT, 8590CT, and 8590CC genotypes were compared descriptively using multiple linear regression adjusting for age, BMI, SBP, and antihypertensive medication. Descriptive *P* values of a 2-tailed *t* test for independent groups for a dominant model (CC+CT versus TT) and a recessive model (CC versus CT+TT) are reported. Furthermore, the creatinine clearance of the individuals according to *CYP4A11* T8590C polymorphism were considered by calculating least square means adjusted for age, BMI, gender, antihypertensive medication, and diabetes. The results of men and women and descriptive *P* values of a 2-tailed *t* test for independent groups for both genetic models are reported.

Results

In total, 684 women and 713 men were genotyped. The allele frequencies of the 8590T and 8590C allele were 86.7% and 13.3%, respectively. The 8590TT, 8590CT, and 8590CC genotypes were found in 75.5%, 22.4%, and 2.1% of the population. These frequencies do not deviate from those

TABLE 1. Baseline Characteristics of the Study Population (MONICA Augsburg Echocardiographic Substudy)

	Men		Women	
Variable	Normotensive	Hypertensive	Normotensive	Hypertensive
n	346	367	402	282
Age, years	46.8±13.2	56.7±12.8	45.2±12.4	59.4±10.0
BMI, kg/m^2	26.0±3.0	28.1±3.7	25.0±4.0	28.8±4.9
SBP, mm Hg	124.4±9.6	149.6±17.3	118.5±11.0	149.7±16.2
DBP, mm Hg	77.0±7.6	88.2±12.2	73.8±8.0	85.4±11.6
Diabetes, %	2.9	8.2	1.7	5.7

Mean values±SD are presented.

TABLE 2. Age and BMI Stratified by T8590C Genotype and the Genotype Distribution in Different Subgroups of the Study Population (MONICA Augsburg Echocardiographic Substudy)

	Genotype		
Variable	TT	CT	CC
n	1055	313	29
Age, years (mean±SD)	51.4±13.67	51.9±13.65	49.9±13.25
BMI, kg/m^2 (mean±SD)	26.8±4.17	26.8±4.30	26.6±3.53
Men, n (%)	532 (74.6)	168 (23.6)	13 (1.8)
Women, n (%)	523 (76.5)	145 (21.2)	16 (2.3)
Diabetes, n (%)	46 (73.0)	16 (25.4)	1 (1.6)
No diabetes, n (%)	1009 (75.6)	297 (22.3)	28 (2.1)

predicted by Hardy–Weinberg equilibrium and were similar to those reported in the study by Gainer et al.[10] The baseline characteristics of the study population, stratified by hypertension status and gender, are shown in Table 1. Age and BMI stratified by T8590C genotype and the genotype distribution in different subpopulations are shown in Table 2. In total, 649 probands (46.5%) were hypertensive.

Effect of the T8590C Polymorphism on Blood Pressure Measurements

Compared with individuals with TT or CT genotype, CC carriers had higher SBP and DBP levels with similar trends in both men and women. In contrast, if CC carriers and CT carriers were combined (ie, assuming a dominant mode of action), no significant differences with regard to blood pressure levels were found compared with TT carriers (Table 3). In both genetic models, no interactions between genotype and covariates (age, BMI, gender, and antihypertensive medications) were found.

When assuming a recessive effect of the C allele, the OR of having hypertension attributable to the CC genotype compared with CT and TT genotype was 3.31 (95% CI, 1.38 to 7.96) in the entire study population (Table 4). No significant interaction between T8590C genotype and gender or any other covariate in the model (age, BMI) was found. These findings indicate that there is no significant difference in the effect of the T8590C genotype on the prevalence of hypertension between men and women.

Assuming a dominant effect of the C allele, there was no significant effect of the C allele on the prevalence of hypertension in the entire study group, whereas in women, some indication for an association with the prevalence of hypertension was found (OR, 1.60; 95% CI, 1.03 to 2.47; P=0.036; Table 5).

Effect of the T8590C Polymorphism on LVM Measurements

In 1122 individuals (559 men and 563 women), echocardiograms of sufficient quality were available. No blood pressure–independent effect of the T8590C polymorphism on LVM measurements could be found regardless of whether a dominant or a recessive effect of the C allele was assumed (Table 6). Analyzing interactions between genotypes (domi-

TABLE 3. SBP and DBP Measurements According the T8590C Genotype, Assuming a Dominant and a Recessive Effect of the C Allele

	Genotype				
Variable	TT	CT	CC	P*	P†
Combined, n	1055	313	29		
SBP, mm Hg	134.3±0.53	134.2±0.97	141.4±3.17	0.61	0.026
DBP, mm Hg	80.7±0.34	80.3±0.63	85.4±2.06	0.89	0.021
Men, n	532	168	13		
SBP, mm Hg	137.6±0.76	136.1±1.35	147.4±4.88	0.66	0.039
DBP, mm Hg	82.9±0.50	81.9±0.88	87.9±3.18	0.56	0.104
Women, n	523	145	16		
SBP, mm Hg	130.9±0.71	132.7±1.35	136.0±4.05	0.16	0.26
DBP, mm Hg	78.4±0.46	78.8±0.88	83.1±2.65	0.38	0.086

Values are least square means±SE. SBP adjusted for age, BMI, gender (combined group), and antihypertensive medications. DBP adjusted for age, BMI, and gender (combined group). Antihypertensive medications were not significant in the model. In combined group and in men, age was not significant in the model.

*2-tailed descriptive P values from t test for independent data for the dominant model (CC+CT vs TT); †2-tailed descriptive P values from t test for independent data for the recessive model (CC vs CT+TT).

TABLE 4. Genotype Distribution of the T8590C Polymorphism in Men and Women Stratified by Presence or Absence of Hypertension and ORs for Hypertension, Assuming a Recessive Effect of the C Allele

	Men		Women	
Variable	Normotensive	Hypertensive	Normotensive	Hypertensive
All individuals	346	367	402	282
Genotype				
8590 TT, n (%)	258 (74.6)	274 (74.7)	316 (78.6)	207 (73.4)
8590 CT, n (%)	85 (24.6)	83 (22.6)	79 (19.7)	66 (23.4)
8590 CC, n (%)	3 (0.9)	10 (2.7)	7 (1.7)	9 (3.2)
8590 C allele frequency	0.13	0.14	0.12	0.15
OR (95% CI), *P* value*	4.30 (1.08–17.15), *P*=0.039		2.93 (0.88–9.84), *P*=0.081	
Combined men and women				
OR (95% CI), *P* value†	3.31 (1.38–7.96), *P*=0.016			
Nondiabetics	336	337	395	266
OR (95% CI), *P* value*	4.11 (1.02–16.62), *P*=0.047		2.98 (0.89–10.02), *P*=0.078	
Combined men and women				
OR (95% CI), *P* value*	3.28 (1.36–7.92), *P*=0.008			

ORs (95% CI) were computed for 8590 CC vs CT+TT (reference), adjusted for age, BMI, and gender (combined group).

*2-tailed descriptive *P* values from WALD-χ^2 test; †2-tailed *P* values from WALD-χ^2 test adjusted according to Bonferroni–Holm.[18]

nant and recessive model) and covariates (age, gender, BMI, SBP, and antihypertensive medications) did not reveal any effects.

Effect of the T8590C Polymorphism on Creatinine Clearance

In 1383 individuals, the creatinine clearance was calculated using Cockcroft–Gault formula. No effect of the T8590C polymorphism on creatinine clearance was found regardless of whether a dominant or a recessive effect of the C allele was assumed (Table 7). Furthermore, the genotype distribution was not different between individuals with mildly impaired renal function (creatinine clearance ≤80 mL/min) and individuals with normal renal function (creatinine clearance >80 mL/min; data not shown).

Discussion

In the present study, we describe an association between the functional T8590C polymorphism (F434S) of the *CYP4A11* gene and hypertension in the MONICA Augsburg echocardiographic substudy. Our results are consistent with a recessive effect of the less frequent C allele resulting in relevant increases of absolute blood pressure values as well as the prevalence of hypertension in our population-based sample. These findings expand the results of the study by Gainer et al, who postulated a significant association with arterial hypertension and the 8590C allele in 2 independent samples (Tennessee Cohort and Framingham Offspring Cohort).[10]

In contrast to Gainer et al, our findings are consistent with a relatively profound recessive rather than dominant mode of action of this loss-of-function variant. In our analyses, abso-

TABLE 5. ORs for Hypertension, Assuming a Dominant Effect of the C Allele of the T8590C Polymorphism

	Men		Women	
Variable	Normotensive	Hypertensive	Normotensive	Hypertensive
All individuals	346	367	402	282
OR (95% CI), *P* value*	0.95 (0.66–1.38), *P*=0.79		1.60 (1.03–2.47), *P*=0.036	
Combined men and women				
OR (95% CI), *P* value†	1.17 (0.89–1.56), *P*=0.27			
Nondiabetics	336	337	395	266
OR (95% CI), *P* value*	0.98 (0.67–1.43), *P*=0.91		1.67 (1.07–2.61), *P*=0.024	
Combined men and women				
OR (95% CI), *P* value*	1.22 (0.91–1.63), *P*=0.18			

ORs (95% CI) were computed for 8590 CC+CT vs TT (reference), adjusted for age, BMI, and gender (combined group).

*2-tailed descriptive *P* values from WALD-χ^2 test; †2-tailed *P* values from WALD-χ^2 test adjusted according to Bonferroni–Holm.[18]

TABLE 6. Effect of the T8590C Polymorphism on LVM Measurements in 1122 Individuals From the MONICA Augsburg Echocardiographic Substudy

	Genotype				
Variable	TT	CT	CC	*P**	*P*†
n	846	252	24		
LVMI, g/m^2	85.5±0.57	86.3±1.05	84.0±3.41	0.65	0.62
Septal wall, mm	10.6±0.06	10.7±0.10	10.5±0.33	0.90	0.72
Posterior wall, mm	8.8±0.04	8.8±0.07	8.9±0.24	0.99	0.69
LVEDD, mm	47.9±0.14	48.2±0.26	47.7±0.86	0.38	0.77
Ejection fraction, %	59.3±0.26	59.0±0.48	58.8±1.55	0.54	0.76

Values are least square means±SE adjusted for age, BMI, SBP, antihypertensive medication, and gender. For LVEDD and ejection fraction, antihypertensive medications and SBP were not significant covariates and withdrawn from the model.

*2-tailed descriptive *P* values from *t* test for independent data for the dominant model (CC+CT vs TT); †2-tailed descriptive *P* values from *t* test for independent data for the recessive model (CC vs CT+TT).

LVMI indicates left ventricular mass index.

lute blood pressure values as well as the number of hypertensive individuals were distributed equally in CT and TT allele carriers. Thus, further studies on larger numbers of individuals and more detailed knowledge on the molecular mechanisms affected by the *CYP4A11* T8590C allele status are required to clarify whether blood pressure is modulated by dominant or recessive inheritance.

Because Gainer et al's study lacks an analysis of absolute blood pressure values in relation to the genotype, our analysis focuses on this phenotype for the first time. In this respect, the present study is remarkable for the extent by which SBP and DBP were elevated in homozygous CC allele carriers of the T8590C polymorphism. In fact, the elevation by ≈7 mm Hg and 5 mm Hg in SBP and DBP is much larger than that observed with most other hypertension-related polymorphisms.[1] Thus, the *CYP4A11* polymorphism may be remarkable for a relatively strong effect for a relatively common variant if this association can be confirmed in further studies. Indeed, our findings indicate that >9 million people in the European Union and 5.8 million in the United States carry a genotype that exposes to a 3.3-fold risk for hypertension.

Phenotypic data of the MONICA Augsburg echocardiographic substudy allow the evaluation of the potential impact of the T8590C polymorphism on LV geometry. No effect of this polymorphism on LVM or geometry was found regardless of whether a dominant or recessive mode of action was assumed. Together, these data let us assume that this polymorphism has a significant effect in regulation of blood pressure, but an additional myocardial effect is unlikely. This may be explained by the renal expression of the gene and the localization of the functional active metabolite 20-HETE in the proximal tubules with yet no evidence of cardiac expression of the gene.

To evaluate the potential impact of genetic variation in the *CYP4A11* gene on renal function, we calculated the creatinine clearance using Cockcroft–Gault formula and tested its association with the T8590C polymorphism. There was no significant effect regardless of whether a dominant or a recessive effect of the C allele was assumed. Within the complex regulation of renal vascular tone and with respect to different cofactors sensitizing the vasoconstrictor activity of 20-HETE,[19] the effect of this polymorphism seems to not be strong enough to modulate renal function. This observation may be important because the present study is the first evaluation of the T8590C polymorphism on renal function in a population-based sample. Unfortunately, we have no information on renal sodium and potassium handling in these individuals. Indeed, 20-HETE excretion may be regulated by salt intake.[20] Specifically, it has been suggested that salt sensitivity of blood pressure may result from impairment of natriuresis mechanism dependent on 20-HETE.[20] Because our large population-based sample lacks phenotypic data about salt intake and salt-sensitive hypertension, our analysis cannot address these important phenotypes.

Limitations

Our study lacks functional data that may explain the mechanism that mediates the association between the *CYP4A11*

TABLE 7. The Creatinine Clearance‡ According to *CYP4A11* T8590C Genotypes in 1383 Individuals From the MONICA Augsburg Echocardiographic Substudy

	Genotype				
Variable	TT	CT	CC	*P**	*P*†
Combined, n	1045	309	29		
Creatinine clearance, mL/min	118.0±0.66	117.4±1.21	114.6±3.95	0.55	0.42
Men, n	527	167	13		
Creatinine clearance, mL/min	123.7±0.89	122.8±1.58	124.6±5.69	0.67	0.85
Women, n	518	142	16		
Creatinine clearance, mL/min	111.9±0.97	111.9±1.85	104.8±5.53	0.71	0.20

Values are least square means±SE adjusted for age, BMI, gender (combined group), antihypertensive medications, and diabetes. In women, diabetes was not a significant covariate and was withdrawn from the model.

*2-tailed descriptive *P* values from *t* test for independent data for the dominant model (CC+CT vs TT); †2-tailed descriptive *P* values from *t* test for independent data for the recessive model (CC vs CT+TT); ‡calculated using Cockcroft–Gault formula.[17]

polymorphism and arterial blood pressure. In this respect, Gainer et al demonstrated by in vitro experiments that the C allele of the T8590C polymorphism results in a phenylalanine to serine replacement that reduces the 20-HETE synthase activity of *CYP4A11* by more than half.[10] In vivo verification of this finding would be of great interest, but in our patient sample, no 24-hour urine was collected. Moreover, more detailed studies on mechanistic implications of the 8590C allele are needed specifically with respect to dietary, preventive, or therapeutic interventions in carriers of this genotype.

Furthermore, association studies require repetitive replication before definitive conclusions can be drawn. In this respect, the *CYP4A11* polymorphism is remarkable for consistent findings in several population-based samples, as well as supportive data from a quantitative trait locus for blood pressure on rat chromosome 5 syntenic to human chromosome 1p33-p35, in which *CYP4A11* is located,[21] and finally, congruent data from *CYP4A14* knockout mice, a gene that is closely related to the human *CYP4A11* gene.[7]

Perspectives

The study by Gainer et al[10] and our data nicely demonstrate that candidate gene association studies can give insights into the unraveling of common and multifactorial phenotypes if stringent criteria for the study design are applied (eg, biological plausibility, rigorous phenotypic and genotypic assessment, appropriate statistical analysis, as well as independent replication).[22]

In fact, the consistence of the present findings with the 2 population samples studied by Gainer et al is indicative for a reproducible finding and allows to speculate that the *CYP4A11* gene is of importance for blood pressure regulation in the human population. Further replication studies focusing on functional phenotypes and on possible pharmacogenetic interactions are needed for a better understanding of the role of *CYP4A11* in the complex regulation of blood pressure.

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