Evaluation of the Aldosterone Synthase (CYP11B2) Gene Polymorphism in Patients With Myocardial Infarction

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Abstract—Left ventricular remodeling after myocardial infarction involves activation of the renin-angiotensin-aldosterone system. Recently, the biallelic −344T/C polymorphism of the aldosterone synthase gene was associated with increased aldosterone levels, arterial hypertension, diastolic dysfunction, and left ventricular dilatation. We hypothesized that this polymorphism may also affect left ventricular geometry and function after myocardial infarction. By using a standardized questionnaire, as well as anthropometric and echocardiographic measurements, we thus studied 606 patients (533 men and 73 women) who had a myocardial infarction before the age of 60 years. The aldosterone synthase gene polymorphism was analyzed after polymerase chain reaction amplification and restriction enzyme digestion. The results demonstrated that there was no association of the aldosterone synthase gene polymorphism with echocardiographically determined left ventricular dimensions, wall thicknesses, or indexes of systolic or diastolic function. Furthermore, anthropometric data, including blood pressure levels, were balanced between the different genotypes. Finally, the allele frequency was similar for patients with myocardial infarction and a sample group from the normal population (n=1675). The data indicate that the allele status of the aldosterone synthase gene polymorphism is not useful for the identification of patients with myocardial infarction who have impaired left ventricular function or unfavorable remodeling. **(*Hypertension*. 2000;35:704-709.)**

Key Words: aldosterone ■ genes ■ myocardial infarction ■ cardiac function ■ echocardiography

Left ventricular (LV) dilatation after myocardial infarction (MI) involves the activation of neurohormonal systems. Specifically, aldosterone levels have been found to be increased in some patients with MI with profound implications for cardiac remodeling and long-term prognosis.[1–3] More recently, it was hypothesized that the variability of aldosterone levels may be also affected by a genetic alteration.[4] Especially, a cytosine/thymidine (C/T) exchange at position −344 in the regulatory region of the aldosterone synthase gene (CYP11B2) was associated with enlargement and disturbed filling of the LV in healthy young white adults,[4] as well as with arterial hypertension in some, but not all, sample groups.[5–7] Furthermore, the aldosterone synthase gene polymorphism has been shown to potentially influence aldosterone levels.[5] Because increased aldosterone levels may be associated with increased LV diameter[4] and LV mass,[6,8–10] we hypothesized that LV remodeling after MI may be affected by this aldosterone synthase gene polymorphism. The aim of the present study was therefore to investigate, first, whether the aldosterone synthase gene polymorphism is associated with poor LV remodeling after MI and, second, whether the aldosterone synthase gene polymorphism is associated with the risk of experiencing MI by comparing the allele frequencies in patients with MI with respective allele frequencies in a large population-based sample.

Methods

Study Population

A total of 609 patients with MI were identified through the population-based Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) MI registry in Augsburg, Germany, and complete phenotypes and genotypes were available for 606 patients with MI. Patients who had an MI before the age of 60 years in the period from 1984 to 1994 were included in the study. From the total of 1254 patients with MI, 580 (46.2%) patients did not respond to our invitation to participate, 65 (5.2%) patients were no longer available (death 2.8%, moving 2.4%), and 609 (48.6%) patients agreed to participate in the study. The echocardiographic examination was performed after a mean of 5.6 years after MI. The clinical diagnoses were validated on the basis of MONICA diagnostic criteria.[11,12] All patients were studied with a questionnaire-based interview and anthropometric measurements. According to the same protocols, 1675 individuals were evaluated in population-based MONICA Augsburg surveys in 1994 to 1995, as described previously.[6,13,14]

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TABLE 1. Anthropometric and Demographic Data of Patients with MI According to the −344C/T Polymorphism in the Aldosterone Synthase Gene

Variable	TT Genotype (n=187)	CT Genotype (n=299)	CC Genotype (n=120)	*P* (ANOVA or χ^2)
Gender, % male	88.2	85.3	90.9	0.65
Age at MI, y	50.6±0.5	50.7±0.4	50.8±0.6	0.81
Transmural MI, %	97.8	94.9	95.7	0.25
Anterior MI, %	44.7	42.4	46.5	0.73
Maximal CK, U/L	743±58	780±45	777±62	0.66
Maximal CK-MB, U/L	69±4	69±3	76±7	0.37
Age at echo study, y	56.3±0.6	56.4±0.4	56.3±0.6	0.94
Time after MI, y	5.5±0.3	5.6±0.2	5.2±0.3	0.92
BMI, kg/m^2	28.6±0.3	28.3±0.2	28.6±0.3	0.89
BSA, m^2	1.957	1.944	1.955	0.38
Heart rate, bpm	67.2±0.8	66.9±0.7	64.6±1.1	0.08
Systolic BP, mm Hg	131.0±1.1	134.0±1.0	129.4±1.4	0.67
Diastolic BP, mm Hg	83.9±0.7	85.1±0.7	82.5±0.9	0.42
Hypertensive, %	57.2	55.6	50.4	0.26
Antihypertensive or antianginal medication, %	97.9	98.3	96.7	0.57
Diabetes mellitus, %	12.8	15.4	17.4	0.26
Total cholesterol, mg/dL*	229.4±3.4	221.8±2.4	223.1±4.0	0.17
LDL-cholesterol, mg/dL*	138.1±2.8	131.7±2.2	129.6±3.6	0.10
HDL-cholesterol, mg/dL*	45.4±1.0	48.4±0.9	47.0±1.2	0.10

TT and CC genotypes indicate homozygosity and CT genotype indicates heterozygosity for the aldosterone synthase (CYP11B2) polymorphism; CK, creatine kinase; CK-MB, creatine kinase, heart-specific isoenzyme; BMI, body mass index; BSA, body surface area; systolic and diastolic BP, systolic and diastolic blood pressure, respectively.

Values are given as mean±SEM.

*To convert values for cholesterol to mmol/L, multiply by 0.02586.

TABLE 2. Echocardiographic Data of Patients with MI According to the −344C/T Polymorphism in the Aldosterone Synthase Gene

	TT Genotype (n=187)	CT Genotype (n=299)	CC Genotype (n=120)	*P* (ANOVA or χ^2)
LV diameter				
Septal wall, mm	10.9±0.2	11.0±0.1	10.8±0.2	0.60
Posterior wall, mm	10.1±0.1	10.0±0.1	10.0±0.1	0.47
LVEDD, mm	55.7±0.6	54.4±0.4	56.7±0.7	0.53
LVESD, mm	41.1±0.6	39.9±0.4	41.8±0.7	0.77
LVM				
LVM, g	288±6.7	276±4.5	291±8.0	0.97
LVMI, g/m$^{2.7}$ height	269±6.1	260±4.1	268±7.6	0.70
LVMI, g/m height	168±3.8	162±2.5	169±4.6	0.89
LVMI, g/m^2 BSA	149±3.5	143±2.2	150±4.1	0.81
LVH, %	62.9	65.2	63.9	0.81
Diastolic function				
E/A ratio	1.0±0.02	1.0±0.02	1.02±0.03	0.29
E/A ratio >1, %	41.5	39.2	40.5	0.82
IVRT, ms	82.3±2.5	78.8±1.7	79.2±2.9	0.34
Systolic function				
Ejection fraction, %	50.6±0.8	51.8±0.5	52.7±0.8	0.06

LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; BSA, body surface area; IVRT, isovolumetric relaxation time. Values are given as mean±SEM.

TABLE 3. Echocardiographic Data of Patients With Anterior and Posterior MI According to the −344C/T Polymorphism in the Aldosterone Synthase Gene

	TT Genotype (n=81)	CT Genotype (n=127)	CC Genotype (n=56)	*P* (ANOVA or χ^2)
Anterior MI (n=264)				
Septal wall, mm	10.5±0.2	10.8±0.1	10.8±0.2	0.45
Posterior wall, mm	9.9±0.1	10.0±0.1	9.8±0.2	0.78
LVEDD, mm	56.6±0.9	55.3±0.6	57.0±1.1	0.91
LVESD, mm	41.7±0.9	40.5±0.6	41.9±1.1	0.99
LVM, g	287±10.9	280±7.1	292±12.3	0.83
E/A ratio	1.02±0.04	1.01±0.04	1.02±0.05	0.70
IVRT, ms	82.2±3.5	81.3±2.7	83.1±4.1	0.91
Ejection fraction, %	50.1±1.1	51.2±0.8	52.6±1.3	0.15
	TT Genotype (n=106)	CT Genotype (n=172)	CC Genotype (n=64)	*P* (ANOVA or χ^2)
Posterior MI (n=342)				
Septal wall, mm	11.2±0.3	11.1±0.2	10.9±0.3	0.48
Posterior wall, mm	10.1±0.2	10.1±0.1	10.1±0.2	0.80
LVEDD, mm	55.4±0.7	53.7±0.5	56.5±0.8*	0.59
LVESD, mm	41.2±0.8	39.4±0.5	41.7±0.9*	0.95
LVM, g	290±9.0	274±6.0	295±11.3	0.98
E/A ratio	0.9±0.03	1.0±0.03	1.02±0.04	0.24
IVRT, ms	82.7±3.7	77.8±2.2	74.1±4.2	0.09
Ejection fraction, %	51.2±1.1	51.9±0.7	53.4±1.1	0.19

TT and CC genotypes indicate homozygosity and CT genotype indicates heterozygosity for the aldosterone synthase (CYP11B2) polymorphism; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; and IVRT, isovolumetric relaxation time.

Values are given as mean±SEM.

*In univariate analysis, significantly greater than CT genotype.

Echocardiography

A 2-dimensionally guided M-mode echocardiogram was performed on each patient of the MONICA MI registry by 1 expert sonographer with 1 recorder (Sonos 1500; Hewlett Packard). Only tracings that demonstrated optimal visualization of LV interferences were used, a requirement that resulted in the exclusion of 6.3% of potential subjects for respective data points. Techniques for M-mode–guided measurements of LV structures, as well as the calculation and indexation of LV mass, were reported previously in detail.[13] Briefly, the Penn Convention criteria were applied for the measurement of LV dimensions and the calculation of LV mass.[15] LV ejection fraction was calculated according to the modified Simpson formula.[16]

Genotyping

DNA was extracted from peripheral lymphocytes according to standard procedures. Genotyping was carried out according to the methods described by Kupari et al.[4] Briefly, DNA samples were amplified in polymerase chain reactions with 10 pmol of both primers (CAGGAGGAGACCCCATGTGAC [sense] and CCTC-CACCCTGTTCAGCCC [antisense]) and the protocol of 35 cycles of denaturation at 94°C for 1 minute, 67°C annealing for 1 minute, and 72°C extension for 2 minutes. After polymerase chain reaction amplification, the fragments were digested with *Hae*III restriction enzyme, followed by separation of the fragments on a 2.5% agarose gel. The uncut −344T allele (wild type) had a size of 273 bp, and cut fragments (C allele) had a size of 202 bp (plus smaller fragments in each case).

Statistical Analysis

According to the aldosterone −344C/T allele status, continuous data were compared with the use of ANOVA and classified values with χ^2 tests, respectively. The effect of the −344C/T allele status on LV mass index, LV end-diastolic dimension, fractional shortening, LV ejection fraction, isovolumetric relaxation period, and ratio of early to late diastolic filling of the LV (E/A ratio) was examined with multiple linear regression analysis after adjustment for age, gender, body mass index, systolic blood pressure, and the use of antihypertensive therapy. Furthermore, the study samples were partitioned by infarct location, gender, age (<55 or ≥55 years), hypertension status, and the presence or absence of hypercholesterolemia, diabetes mellitus, cigarette smoking, or LV hypertrophy. LV hypertrophy was defined as an LV mass index of ≥134 g/m^2 in men or ≥110 g/m^2 in women. Hypertension was defined as systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg or when antihypertensive medication was taken on regular basis. In multivariate regression analysis, the corresponding β-coefficients were computed. At an α error of 5%, the present study sample provided a power of 78.7% to detect a difference in LV end-diastolic diameter of 1.12 mm between the respective genotype groups. Probability values are reported for each test and statistical model.

Results

The anthropometric data for patients with MI are shown in Table 1. In individuals from the MI registry (total 606: 533 men, 73 women), the frequencies of the aldosterone synthase genotypes were in Hardy-Weinberg equilibrium. There was

TABLE 4. Multiple Linear Regression: Influence of the Aldosterone Synthase Gene Polymorphism on Structure and Function of the LV in Patients With MI

	β-Coefficient†	P
All patients with MI (n=606)*		
LVMI, g/m²	−0.004	0.72
LVEDD, mm	+0.45	0.46
Ejection fraction, %	+0.41	0.23
IVRT, ms	−1.61	0.15
E/A	+0.09	0.34
Patients with MI without treatment with diuretics, β-blockers, calcium antagonists, or ACE inhibitors (n=81)‡		
LVMI, g/m²	+0.08	0.50
LVEDD, mm	−0.07	0.57
Ejection fraction, %	+0.10	0.45
IVRT, ms	−0.16	0.19
E/A	+0.16	0.16
Patients with MI with treatment with diuretics, β-blockers, calcium antagonists, ACE inhibitors, or a combination (n=525)‡		
LVMI, g/m²	−0.01	0.83
LVEDD, mm	+0.03	0.47
Ejection fraction, %	+0.01	0.09
IVRT, ms	−0.03	0.45
E/A	+0.04	0.39

*Adjusted for age, gender, systolic blood pressure, antihypertensive medication, and localization of MI.

†Change in respective units by the effects of aldosterone synthase gene polymorphism.

‡Adjusted for age, gender, systolic blood pressure, and localization of MI.

See Table 2 for abbreviations.

no difference in systolic or diastolic functional parameters of the LV in the aldosterone synthase polymorphism genotype groups (Tables 1, 2, and 3). Grouping of the diastolic parameters, such as E/A ratio >1 or isovolumetric relaxation time in quartiles, showed no differences in the genotype groups. Furthermore, neither univariate analysis (Table 2) nor multivariate analysis (Table 4) showed any statistically significant difference in LV end-diastolic dimension, LV wall thickness, or LV mass associated with the aldosterone synthase genotype groups. Given that the location of the MI affects the remodeling of infarcted and noninfarcted walls differently, we analyzed patients with anterior (n=264) and posterior (n=342) MI separately. However, LV wall thicknesses, LV diameters, and LV mass, as well as systolic and diastolic LV function, also were not affected by the −344T/C aldosterone synthase gene polymorphism in these subgroups (Table 3).

To examine possible effects of the polymorphism in specific subgroups, we divided the MI patient sample according to the presence or absence of coronary risk factors. No significant influence could be demonstrated on LV end-diastolic diameter (Tables 5 and 6) or other structural or functional parameters that were examined (data not shown). Furthermore, the percentage of patients using ACE inhibitors, diuretics, β-blockers, calcium antagonists, antiplatelet medication, or anticoagulant medication was similar in the different genotype groups (data not shown).

In the population-based survey sample (total 1675: 825 men, 850 women), the frequencies of the aldosterone synthase −344C allele were also in Hardy-Weinberg equilibrium and were similar to those in patients with MI (0.45 and 0.44 in men and 0.43 and 0.47 in women, respectively; P=NS). Likewise, the −344TT, −344CT, and −344CC genotypes were found at similar frequencies in patients with MI and in participants of the population-based survey, respectively (Table 6). 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 into subgroups

TABLE 5. Presence of Cardiovascular Risk Factors in Patients With MI According to the −344C/T Polymorphism in the Aldosterone Synthase Gene

Risk Factor	TT Genotype (n=187)	CT Genotype (n=299)	CC Genotype (n=120)	P (ANOVA or χ^2)
Arterial hypertension				
Blood pressure >140/90 mm Hg	(n=62)	(n=119)	(n=42)	
LVEDD, mm	55.5	54.1	56.1	0.20
Blood pressure <140/90 mm Hg	(n=125)	(n=180)	(n=78)	
LVEDD, mm	55.8	54.6	56.9	0.34
Hypercholesterolemia				
LDL cholesterol >100 mg/dL*	(n=158)	(n=229)	(n=89)	
LVEDD, mm	55.9	54.4	57.4	0.13
LDL cholesterol <100 mg/dL*	(n=29)	(n=70)	(n=31)	
LVEDD, mm	54.8	54.3	54.3	0.94
Diabetes mellitus†	(n=30)	(n=51)	(n=22)	
LVEDD, mm	56.0	53.6	56.0	0.20
No diabetes mellitus†	(n=157)	(n=248)	(n=98)	
LVEDD, mm	55.6	54.6	56.7	0.25
Current cigarette smoking	(n=31)	(n=47)	(n=13)	
LVEDD, mm	55.3	54.6	54.2	0.91
No or former smoking	(n=156)	(n=252)	(n=107)	
LVEDD, mm	55.8	54.4	56.9	0.23

*To convert values for cholesterol to mmol/L, multiply by 0.02586.

†Blood sugar >180 mg/dL, HbA1c >6.5%, or antidiabetic medication.

TABLE 6. Frequencies of the Aldosterone Synthase Gene Polymorphism in Normal Population and in Patients With MI in All Individuals and in Different Subgroups

Individuals Examined	Normal Population (n=1675)	Patients With MI (n=606)	*P* (χ^2)
All individuals			
TT genotype, %	30.9	29.0	
CT genotype, %	49.3	49.4	0.84
CC genotype, %	19.8	21.6	
Arterial hypertension			
Blood pressure >140/90 mm Hg	(n=593)	(n=223)	
TT genotype, %	29.8	28.3	
CT genotype, %	48.4	52.5	0.56
CC genotype, %	21.8	19.3	
Blood pressure <140/90 mm Hg	(n=946)	(n=383)	
TT genotype, %	28.4	32.4	
CT genotype, %	50.1	47.3	0.36
CC genotype, %	21.5	20.4	
Hypercholesterolemia			
LDL-cholesterol >100 mg/dL*	(n=1227)	(n=477)	
TT genotype, %	28.0	33.1	
CT genotype, %	49.7	48.2	0.07
CC genotype, %	22.2	18.7	
LDL-cholesterol <100 mg/dL*	(n=312)	(n=129)	
TT genotype, %	32.7	22.5	
CT genotype, %	48.4	52.7	0.08
CC genotype, %	18.9	24.8	
Diabetes mellitus†	(n=59)	(n=101)	
TT genotype, %	25.4	29.7	
CT genotype, %	54.2	47.5	0.71
CC genotype, %	20.3	22.8	
No diabetes mellitus†	(n=1480)	(n=505)	
TT genotype, %	29.1	31.1	
CT genotype, %	49.3	49.5	0.50
CC genotype, %	21.6	19.4	
Current cigarette smoking	(n=382)	(n=90)	
TT genotype, %	29.8	35.6	
CT genotype, %	49.2	50.0	0.31
CC genotype, %	20.9	14.4	
No or former smoking	(n=1157)	(n=516)	
TT genotype, %	28.7	30.0	
CT genotype, %	49.5	49.0	0.84
CC genotype, %	21.8	20.9	

*To convert values for cholesterol to mmol/L, multiply by 0.02586.
†Blood sugar >180 mg/dL, HbA1c >6.5%, or antidiabetic medication.

defined by the presence or absence of coronary risk factors (Table 6). Given the limitations of such case-control analysis, we examined whether the lack of difference in allele frequencies between the MI registry and the survey population might be explained by differences in the size or location of infarctions or the age at the time of infarction (ie, factors that might affect survival after infarction). However, the lack of association between the aldosterone synthase gene polymorphism and MI could not be explained by differences in genotype groups with respect to the time that had elapsed between the first MI and presentation at the study center (Table 1) or by differences in the age at the time of the MI or in the localization or size of the MI (Table 3).

Discussion

A strong association between the −344C allele of the aldosterone synthase gene polymorphism and increased LV diameter and LV mass, as well as impaired diastolic function, has been reported in a previous study of 84 young and healthy individuals.[4] In the present study, no such associations were found in a large number of long-term survivors of MI. Moreover, the aldosterone synthase −344C/T allele frequencies were equally distributed in a population-based sample and in the present sample of patients with MI. Along with similar distributions of MI size and location in various genotype groups, these data may indicate that there is no strong association between the aldosterone synthase gene polymorphism and the risk of experiencing MI as well as the risk of presenting with poor remodeling after MI.

The discrepancy of the previous positive[4] and the present negative results may be explained by the fact that the previous study was conducted with apparently healthy young individuals, whereas the present study was conducted with patients with MI. Most of the present study patients were taking antihypertensive medication, including ACE inhibitors and β-blockers, that might affect aldosterone levels. Furthermore, ethnic differences between the previous (Finnish) and the present (German) population samples may account for the differences. This point may be of specific relevance if the −344 allele status is a marker for another genetic alteration. In particular, the aldosterone synthase gene locus may be in close proximity to such causal mutation, which occurs, therefore, in linkage disequilibrium with the −344T/C polymorphism, at least in the isolate Finnish population.[17]

Albeit the differences in the design between the previous[4] and the present study may account for the different results, these data are not in favor of a strong influence of the aldosterone synthase −344C/T polymorphism on LV size and function in a western European population. First, the aldosterone synthase gene polymorphism has no proved effect on potential intermediate phenotypes such as increased serum aldosterone levels or increased blood pressure that might affect cardiac remodeling. Specifically, data on the association with serum aldosterone levels are discrepant, with 1 study showing the highest levels in the CC genotype group,[18] 2 studies showing the highest levels in the TT genotype group,[7,19] and 1 study showing no association.[6] Moreover, data on the association with blood pressure levels are largely negative, including the present study on patients with MI.[4,6,8,9,18] This may be of interest because other known mutations of the aldosterone synthase gene have in common an affect on both aldosterone levels and blood pressure.[20] Second, the allele status of the aldosterone synthase gene

polymorphism had no effect on LV size and function in a large population-based sample.[6]

A limitation of the present study is that only survivors of MI were included. Thus, the apparent lack of association might result from LV dilatation and poor prognosis that occur in patients with sudden or early death after MI. Although this limitation cannot be excluded in any patient population that has been sampled after MI, selection by survival is unlikely because, first, the distribution of aldosterone synthase genotypes was equal in patients with MI and a large population-based sample and, second, there was no relation between allele status and age at MI, size or location of MI, or time elapsed since MI and the echocardiographic study.

Therefore, on the basis of the anthropometric and echocardiographic data and the examination of the aldosterone synthase gene polymorphism in patients with MI and a large population-based sample, we conclude that this polymorphism is not a strong risk factor for MI and does not appear to influence LV remodeling after MI.

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References

1. Rouleau JL, Packer M, Moye L, de Champlain J, Bichet D, Klein M, Rouleau JR, Sussex B, Arnold JM, Sestier F. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. *J Am Coll Cardiol*. 1994;24:583–591.
2. White PC. Disorders of aldosterone biosynthesis and action. *N Engl J Med*. 1994;331:250–258.
3. Weber KT, Sun Y, Campbell SE, Slight SH, Ganjam VK, Griffing GT, Swinfard RW, Diaz-Arias AA. Chronic mineralocorticoid excess and cardiovascular remodeling. *Steroids*. 1995;60:125–132.
4. Kupari M, Hautanen A, Lankinen L, Koskinen P, Virolainen J, Nikkila H, White PC. Associations between human aldosterone synthase (CYP11B2) gene polymorphisms and left ventricular size, mass, and function. *Circulation*. 1998;97:569–575.
5. Tamaki S, Iwai N, Tsujita Y, Kinoshita M. Genetic polymorphism of CYP11B2 gene and hypertension in Japanese. *Hypertension*. 1999;33:266–270.
6. Schunkert H, Hengstenberg C, Holmer SR, Broeckel U, Luchner A, Muscholl MW, Kürzinger S, Döring A, Hense HW, Riegger GAJ. Lack of association between a polymorphism of the aldosterone synthase gene and left ventricular structure. *Circulation*. 1999;99:2255–2260.
7. Brand E, Chatelain N, Mulatero P, Fery I, Curnow K, Jeunemaitre X, Corvol P, Pascoe L, Soubrier F. Structural analysis and evaluation of the aldosterone synthase gene in hypertension. *Hypertension*. 1998;32:198–204.
8. Duprez DA, Bauwens FR, De Buyzere ML, De Backer TL, Kaufman JM, Van Hoecke J, Vermeulen A, Clement DL. Influence of arterial blood pressure and aldosterone on left ventricular hypertrophy in moderate essential hypertension. *Am J Cardiol*. 1993;71:17A–20A.
9. Navarro-Lopez F, Coca A, Pare JC, de la Sierra A, Bosch X, Urbano Marquez A. Left ventricular hypertrophy in asymptomatic essential hypertension: its relationship with aldosterone and the increase in sodium-proton exchanger activity. *Eur Heart J*. 1993;14(suppl J):38–41.
10. Muscholl M, Schunkert H, Muders F, Elsner D, Kuch B, Hense HW, Riegger GAJ. Neurohormonal activity and left ventricular geometry in patients with essential arterial hypertension. *Am Heart J*. 1998;135:58–66.
11. Löwel H, Lewis M, Hörmann A, Keil U. Case finding, data quality aspects, and comparability of myocardial infarction registers: results of a Southern German register study. *J Clin Epidemiol*. 1991;44:249–260.
12. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case fatality rates in 38 populations from 21 countries in four continents. *Circulation*. 1994;90:583–612.
13. Muscholl M, Hense HW, Bröckel U, Döring A, Riegger GAJ, Schunkert H. Alterations of left ventricular geometry and function in subjects with white coat hypertension. *BMJ*. 1998;317:565–570.
14. Schunkert H, Hense HW, Danser J, Muscholl M, Luchner A, Riegger AJG. Association between circulating components of the renin-angiotensin-aldosterone system and left ventricular mass. *Heart*. 1997;77:24–31.
15. Devereux RB, Reicek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation*. 1977;55:613–618.
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutfesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for the quantification of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr*. 1989;2:358–367.
17. Cavalli-Sforza LL, Piazza A. Human genomic diversity in Europe: a summary of recent research and prospects for the future. *Eur J Hum Genet*. 1993;1:3–18.
18. Pojoga L, Gautier S, Blanc H, Guyene TT, Poirier O, Cambien F, Benetos A. Genetic determination of plasma aldosterone levels in essential hypertension. *Am J Hypertens*. 1998;11:856–860.
19. Davies E, Holloway CD, Ingram MC, Inglis GC, Friel EC, Morrison C, Anderson NH, Fraser R, Connell JMC. Aldosterone excretion rate and blood pressure in essential hypertension are related to polymorphic differences in the aldosterone synthase gene CYP11B2. *Hypertension*. 1999;33:703–707.
20. Lifton RP, Dluhy RG, Powers M, Rich GM, Gutkin M, Fallo F, Gill JR Jr, Feld L, Ganguly A, Laidlaw JC, Murnagham DJ, Kaufman C, Stockigt JR, Ulrick C, Lalouel JM. Hereditary hypertension caused by chimaeric gene duplications and ectopic expression of aldosterone synthase. *Nat Genet*. 1992;2:66–74.

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