Single nucleotide polymorphisms predict the change in left ventricular mass in response to antihypertensive treatment

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Background **Our aim was to determine whether the change in left ventricular (LV) mass in response to antihypertensive treatment could be predicted by multivariate analysis of single nucleotide polymorphisms (SNPs) in candidate genes reflecting pathways likely to be involved in blood pressure control.**

Methods **Patients with mild to moderate primary hypertension and LV hypertrophy were randomized in a double-blind fashion to treatment with either the angiotensin II type 1 receptor antagonist irbesartan ($n = 48$) or the β_1 adrenoreceptor blocker atenolol ($n = 49$). A microarray-based minisequencing system was used for genotyping 74 SNPs in 25 genes. These genotypes were related to the change in LV mass index by echocardiography, after 12 weeks treatment as monotherapy, using stepwise multiple regression analysis.**

Results **The blood pressure reductions were similar and significant in both treatment groups. Two SNPs in two separate genes (the angiotensinogen T1198C polymorphism, corrsponding to the M235T variant and the apolipoprotein B G10108A polymorphism) for those treated with irbesartan, and the adrenoreceptor α_{2A} A1817G for those treated with atenolol, significantly predicted the change in LV mass. The predictive power of these SNPs was independent of the degree of blood pressure reduction.**

Conclusion **SNPs in the angiotensinogen, apolipoprotein B, and the α_2 adrenoreceptor gene predicted the change in LV mass during antihypertensive therapy. These results illustrate the potential of using microarray-based technology for SNP genotyping in predicting individual drug responses. *J Hypertens* 22:2321–2328 © 2004 Lippincott Williams & Wilkins.**

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Introduction

Hypertension is prevalent, affecting approximately 20–25% of the adult population in the Western world [1]. By treating hypertension and factors that contribute to cardiovascular disease, both mortality and morbidity can be reduced. Left ventricular (LV) hypertrophy has attracted much attention, as it constitutes one of the most powerful independent risk factors for cardiovascular morbidity and mortality both in the general population [2], but in particular in hypertensives [3–5]. Moreover, regression of LV hypertrophy may be associated with an improved prognosis [6,7].

Both hypertension and LV hypertrophy are multifactorial diseases. Interestingly, LV hypertrophy has been shown to precede, and has been proposed to contribute to, the development of hypertension [8–11]. This is most likely an expression of its multifactorial nature, in which hemodynamic, neurohormonal and genetic factors are causative. Analyses of juvenile twins have estimated the inter-individual variability of LV hypertrophy to be strongly determined by inherited factors [12,13], a finding also supported by data from the Framingham Heart Study [14].

Only part of the change in LV mass in response to antihypertensive treatment can be explained by the change in blood pressure. In addition, there is a large inter-individual variation in the response to antihypertensive treatment [15] and the individual patient's response, measured either as change in blood pressure or in LV mass, is not possible to predict. Previously, we found associations between individual gene polymorphisms in the renin–angiotensin–aldosterone system and

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the change in LV mass in response to specific antihypertensive treatment [16]. However, multiple pathophysiological pathways are involved and there is no simple way to discern which specific pathway gives rise to hypertension or LV hypertrophy for a given individual. We have therefore chosen to analyze a panel of 74 single nucleotide polymorphisms (SNPs) in 25 genes involved in cardiovascular pathways. Using this approach, we have previously studied the antihypertensive response, measured as blood pressure reduction [17,18]. In the current study, the genotypes were related to the antihypertensive response when measured as the change in LV mass.

Methods

Study population

The study sample came from the SILVHIA (Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol) trial [19], which was a multicenter trial designed to evaluate the efficacy of the AT_1 receptor antagonist irbesartan, in comparison with the β_1 adrenoreceptor blocker atenolol, on the change in LV mass in hypertensive patients during optimal blood pressure control. A total of 115 patients were randomized to receive 150 mg irbesartan or 50 mg atenolol once daily as monotherapy, in a double-blinded fashion. The dose was doubled after 6 weeks if the diastolic blood pressure was equal to or exceeded 90 mmHg. Following randomization, 14 patients discontinued the trial. DNA and echocardiographic data were available from 97 subjects. The data presented here relate to the change in LV mass index after 12 weeks' treatment as monotherapy.

Blood pressure measurements

Men and women above the age of 18 with primary mild to moderate hypertension and LV hypertrophy, verified by echocardiography, were enrolled. All antihypertensive agents were withdrawn before the start of a 4–6 week, single-blind, placebo lead-in period. The inclusion criteria for hypertension constituted a diastolic blood pressure of 90–115 mmHg at two examinations within 1 week, with values differing by no more than 8 mmHg. Secondary hypertension was excluded by physical examination and appropriate laboratory analyses. All patients were Caucasians.

Blood pressure was measured by trained nurses, using a mercury sphygmomanometer, after the patients had rested for at least 10 min in the seated position, and was determined as the average of three measurements taken 1 min apart. During treatment, blood pressure was measured at trough (24 ± 3 h after the last dose).

Echocardiography

Echocardiography was performed with the patient in the left semilateral position. The ultrasound devices used were the Acuson 128 X P/10 (Mountain View, California, USA), Vingmed CFM 750 (Vingmed Sound, Horten, Norway) and HP SONOS 2500 (Hewlett Packard, Andover, Massachusetts, USA). Measurements were performed on three to five consecutive beats, from which mean values were calculated. Basic measurements of LV dimensions in diastole, and intraventricular septum thickness and posterior wall thickness, were made by M-mode technique. The Penn convention was used for calculation of left ventricular mass, which was corrected for body mass index [20]. The body weight was the actual weight, measured in conjunction with each echocardiographic examination. LV hypertrophy was considered present if LV mass index was $> 131\ g/m^2$ for men and $> 100\ g/m^2$ for women [21]. For reproducibility and other details, see Malmqvist *et al.* [19].

The appropriate university ethics committees approved this study. The patients gave informed consent and the study was performed in accordance with institutional guidelines.

Genotyping

The candidate genes were identified from the literature and the dbSNP (www.ncbi.nlm.nih.gov/SNP) and TSC (the SNP consortium, http://snp.cshl.org/) databases. The candidate genes were chosen based on their function in the renin–angiotensin–aldosterone, the adrenergic and the endothelial systems, and in lipid metabolism. A panel of 74 genetic variants in these genes was chosen (see Table 1).

The 49 fragments comprising 74 SNPs were amplified in eight multiplex polymerase chain reactions (PCRs) containing 2–10 primer pairs in each reaction. The SNPs were genotyped with the DNA polymerase assisted minisequencing single nucleotide primer extension reaction in a microarray format, a system allowing for multiplex analysis of many SNPs and samples in parallel. In the minisequencing reaction, SNP-specific primers are extended with fluorescently labeled dideoxynucleotides, and the ratio between the fluorescence signal from one of the alleles and the sum of the fluorescence signals from both possible alleles at each SNP site was calculated to assign the genotypes. The genotyping system and its validation was previously described in detail in Liljedahl *et al.* [17].

Statistical analyses

Hardy–Weinberg equilibrium was assessed by comparison of the observed and expected genotype frequencies, using the χ^2 test with one degree of freedom, for the SNPs with a frequency greater than 5% for the minor allele.

The change in blood pressure and LV mass index after

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Table 1 Description of the single nucleotide polymorphisms (SNPs) analyzed in the study

Gene name and acronym	Accession number[a]	SNP name[b,c]	dbSNP ID[d]	Amino acid
Renin–angiotensin–aldosterone system				
Aldosterone synthase (CYP11B2)	D13752	CYP11B2 T267C (344T/C)	rs1799998	
Angiotensin-converting enzyme (ACE)	AF118569	ACE C10514T	rs4316	
	AF118569	ACE T10527C	rs4317	Ser/Ala
	AF118569	ACE A10578G	rs4318	Ser/Gly
	AF118569	ACE G12257A	rs4331	
	AF118569	ACE G14480C	rs4341	
	AF118569	ACE C14488A	rs4342	
	AF118569	ACE A14521G	rs4343	Thr/Thr
Angiotensinogen (AGT)	M24686	AGT C1015T (T174M)	rs4762	Thr/Met
	M24686	AGT T1198C (M235T)	rs699	Met/Thr
	M24686	AGT A1237G	NA	Tyr/Cys
	X15323	AGT A1204C (A-20C)	rs5050	
	X15323	AGT G1218A (G-6A)	rs5051	
Angiotensin II type 1 receptor (AGTR1)	AF245699	AGTR1 A49954G	rs5183	Pro/Pro
	AF245699	AGTR1 A50058C (A1166C)	rs5186	
	AF245699	AGTR1 T4955A	rs275651	
	AF245699	AGTR1 T5052G	rs275652	
	AF245699	AGTR1 C5245T	rs1492078	
Angiotensin II type 2 receptor (AGTR2)	U20860	AGTR2 G1675A	rs1403543	
	U20860	AGTR2 G4297T	rs5193	
	U20860	AGTR2 A4303G	rs5194	
Mineralocorticoid receptor (MLR)	M16801	MLR C1825T	NA	Arg/Term
Renin (REN)	M26900	REN T1456G	rs5707	
	M26900	REN A1442G	rs5706	
	M26440	REN G134A	NA	
	M26440	REN T164G	NA	
	M26900	REN A279C (A204C)	rs5705	Thr/Thr
Adrenergic system				
Adrenergic α_{1A} receptor (ADRA1A)	NM_000680	ADRA1A T1441C	NA	Arg/Cys
Adrenergic α_2 receptor (ADRA2A)	M23533	ADRA2A C787G	rs1800544	
	M23533	ADRA2A G1817A	rs1800545	
	M23533	ADRA2A G278T	rs1800763	
Adrenergic β_1 receptor (ADRB1)	AF169006	ADRB1 C1165G	rs1801253	Arg/Gly
	AF169006	ADRB1 A145G	rs1801252	Gly/Ser
Adrenergic β_2 receptor (ADRB2)	J02960	ADRB2 T1217C	rs1042711	Arg/Cys
	J02960	ADRB2 T1244C	rs1801704	
	J02960	ADRB2 G1309A (G46A)	rs1042713	Arg/Gly
	J02960	ADRB2 G1342C (G79C)	rs1042714	Glu/Gln
Adrenergic β_3 receptor (ADRB3)	X72861	ADRB3 T827C	rs4994	Trp/Arg
	X72861	ADRB3 C3246T	rs4999	
Endothelial system				
Endothelin receptor type A (EDNRA)	D11149	EDNRA T89C	rs5333	His/His
	D11149	EDNRA G125A	rs5334	Glu/Glu
Endothelin receptor type B (EDNRB)	D13165	EDNRB G40A	rs5351	Leu/Leu
Endothelial nitric oxide synthase (ENOS)	D26607	eNOS G7002T	rs1799983	Asp/Glu
	AF032908	eNOS A2000T	rs1800783	
	D26607	eNOS G9767A	rs1800780	
	D26607	eNOS A498G	rs1800779	
	D26607	eNOS G20455T	rs1065299	
	D26607	eNOS G2996A	rs1800781	
Lipid metabolism				
Apolipoprotein A (APOA)	J02758	APOA A1449G	rs5092	Thr/Thr
Apolipoprotein B (APOB)	M19828	APOB G10108A (R3611Q)	rs1801701	Arg/Gln
	M19810	APOB C711T	rs1367117	Thr/Ile
Apolipoprotein E (APOE)	M10065	APOE T3932C (T112C)	rs429358	Arg/Cys
	M10065	APOE C4070T (C158T)	rs7412	Arg/Cys
Cholesteryl ester transfer protein (CETP)	U85248	CETP A128C	NA	
	U85248	CETP C146A	rs1800776	
	U85248	CETP C147A	rs1799851	
	M32997	CETP A1300G	rs5882	Ile/Val
	M32997	CETP G1335A	rs5886	Val/Val
	M32998	CETP G338A	rs1800777	Arg/Gln
	M32998	CETP G571A	rs5887	Val/Met
	M32998	CETP A311G	rs2303790	Asp/Gly
Low-density lipoprotein receptor (LDLR)	AF217403	LDLR C16730T	rs688	Asn/Asn
	AF217403	LDLR T20001C	rs5925	Val/Val
Lipase hepatic (LIPC)	M35429	LIPC G89A	NA	Arg/His
	M35429	LIPC A110G	rs6083	Asn/Ser
Lipoprotein lipase (LPL)	AF050163	LPL C9040G	rs328	Ser/Term
	AF050163	LPL G7315C	rs312	
	AF050163	LPL A7344G	rs313	
	AF050163	LPL G7360A	rs314	

(*continued overleaf*)

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Table 1 (*continued*)

Gene name and acronym	Accession number[a]	SNP name[b,c]	dbSNP ID[d]	Amino acid
Other				
Calcium sensing receptor (CASR)	X81086	CASR C3031G	rs1801726	Gln/Glu
	X81086	CASR G2956T	rs1801725	Ala/Ser
Peroxisome proliferator activated receptor alpha (PPARA)	AL078611	PPARA T39067C	rs1800234	Val/Ala
Peroxisome proliferator activated receptor gamma (PPARG)	L40904	PPARG G1043A	NA	Val/Met
	L40904	PPARG C1575T	NA	Pro/Leu

[a]Accession number of GenBank entry. [b]SNP name composed of acronym, nucleotide variation and nucleotide position. Alternative SNP name in parentheses. [c]SNPs marked with parentheses were excluded from the genotyping panel. [d]dbSNP ID number. NA, not available.

12 weeks' treatment was calculated as the relative change compared to baseline measurements. Data are presented as mean values ± SD, where appropriate. A probability (P) value < 0.01 was considered significant in order to reduce the impact of multiple testing. Two-tailed significance levels were used.

The relationship between the genotypes of the 74 SNPs and the change in LV mass index was first analyzed using factorial one-way ANOVA (Statview 5; SAS Institute Inc. Cary, North Carolina, USA) in the irbesartan and atenolol group separately.

The SNPs showing $P < 0.10$ were entered as independent variables in forward stepwise multiple-regression models, with the relative change of LV mass index as the dependent variable. The change in blood pressure was forced into the regression model, since the change in LV mass index is known to be associated with the change in blood pressure.

Results

Basic characteristics and blood pressure and LV mass index response to treatment are presented in Table 2. No significant differences were seen in the two treatment groups regarding age, gender, blood pressure or LV mass index at baseline.

After 12 weeks' treatment, similar significant reductions in blood pressure were achieved in both treatment groups, see Table 2. The mean reduction in LV mass index tended to be greater for those treated with irbesartan compared to those treated with atenolol ($P = 0.10$, Table 2). Dose adjustments, according to protocol, were needed by 66% of the patients treated with irbesartan and 39% of those treated with atenolol. The mean doses of irbesartan and atenolol, at 12 weeks, were 247 and 72 mg, respectively. However, the doses of irbesartan and atenolol were not significantly related to the changes in blood pressure or LV mass index at 12 weeks, and were therefore not considered as confounders in the following analyses. The change in systolic blood pressure was related to the change in LV mass index in the entire sample ($P = 0.003$, by univariate analysis).

The assigned genotypes conformed to Hardy–Weinberg expectations, with the exception of the three SNPs in the AT_2 receptor gene, the C1165G SNP in the β_1 adrenoreceptor gene and the G134A SNP in the renin gene ($P < 0.001$).

The genotypes associated with LV mass index with $P < 0.10$ in univariate analyses are presented in Table 3. Only the angiotensinogen A1218G (which is

Table 2 Basic characteristics and response in blood pressure response and left ventricular (LV) mass to treatment

	Irbesartan (mean values ± SD)	Atenolol (mean values ± SD)	*P* value
Number of patients	48	49	
Age (years)	54 ± 8	54 ± 8	0.94
Gender (proportion females)	37%	31%	0.36
Height (m)	1.74 ± 0.09	1.73 ± 0.09	0.61
Weight (kg)	83 ± 15	82 ± 14	0.73
Pretreatment SBP (mmHg)	164 ± 18	160 ± 20	0.40
Pretreatment DBP (mmHg)	104 ± 7	103 ± 8	0.43
Change in SBP at 12 weeks (mmHg)	−17 ± 19	−11 ± 16	0.13
Change in DBP at 12 weeks (mmHg)	−10 ± 10	−12 ± 8	0.34
Pretreatment LVMI (g/m^2)	148 ± 33	145 ± 27	0.58
LVMI at 12 weeks (g/m^2)	140 ± 30	144 ± 30	0.57
Change in LVMI after 12 weeks (g/m^2)	−8 ± 20	−1 ± 19	0.10

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index.

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Table 3 Change in left ventricular mass index after 12 weeks' treatment with either irbesartan or atenolol, in relation to single nucleotide polymorphisms (SNPs). Mean values ± SD for all polymorphisms with $P < 0.10$ in either treatment group

Genotype (*n*)	ΔLVMI (g/m²)	*P* value
Irbesartan treatment		
ACE 10578 AA (43)	−7 ± 18	0.09
AG (1)	−66	
AGT 174 TT (37)	−4 ± 17	0.07
TM (9)	−16 ± 24	
AGT 235 MM (12)	+3 ± 13	0.04
MT (26)	−10 ± 18	
TT (6)	−23 ± 28	
AGT 1237 AA (43)	−7 ± 18	0.09
GG (1)	−66	
AGT 1218 GG (13)	+5 ± 14	0.009
AG (23)	−13 ± 17	
AA (8)	−15 ± 28	
ApoB 10108 GG (32)	−12 ± 21	0.06
AG (11)	+3 ± 14	
AA (1)	+1	
CASR 2956 GG (30)	−8 ± 17	0.07
GT (13)	−11 ± 25	
TT (1)	+27	
CETP 1336 GG (43)	−7 ± 18	0.09
AG (1)	−66	
EDNRA 125 GG (18)	−16 ± 23	0.04
AG (21)	±0 ± 14	
AA (5)	−10 ± 20	
ADRA2A 278 GG (40)	−10 ± 20	0.09
GT (3)	+11 ± 12	
TT (1)	+11	
AT1R 49954 AA (41)	−7 ± 20	0.05
AG (2)	−3 ± 17	
GG (1)	−47	
Atenolol treatment		
ADRA2A 1817 GG (40)	−4 ± 18	0.03
GA (4)	+20 ± 21	
AA (2)	+13 ± 26	
AGT 1204 AA (35)	−1 ± 18	0.03
CA (8)	−8 ± 23	
CC (3)	+24 ± 8	
REN 134 AA (31)	+3 ± 18	0.03
AG (6)	+4 ± 29	
GG (10)	−15 ± 10	
VDR CC (19)	−8 ± 14	0.05
CT (21)	+7 ± 23	
TT (6)	−6 ± 12	

P values denote the difference in the relative change of left ventricular mass index (LVMI) induced by treatment, in relation to genotype group. ΔLVMI, the change in left ventricular mass index (g/m²) after 12 weeks of antihypertensive treatment.

synonymous with A-6G, the alternative nomenclature depends on which database is used) polymorphism showed a significant association with the change in LV mass index after 12 weeks of irbesartan treatment ($R = 0.30$, $P = 0.009$).

In a stepwise multiple regression analysis, relating the genotypes associated with the change in LV mass index with a $P < 0.10$ by univariate analysis (see Table 3), two SNPs for irbesartan (the angiotensinogen T1198C corresponding to the M235T variant and the apolipoprotein B G10108A polymorphism corresponding to the R3611Q variant) and one SNP for atenolol (the α_{2A} adrenoreceptor G1817A polymorphism) appeared as significant independent predictors of the change in LV mass index in response to treatment (Table 4). With

Table 4 Stepwise multiple regression analysis relating genotypes to the change in left ventricular mass index (LVMI) during treatment with irbesartan or atenolol

Genotype	Regression coefficient	*t*-value	*P* value
Irbesartan treatment			
SBP change	0.33	1.58	0.12
DBP change	0.32	1.22	0.22
AGT 235 TT	−0.098	2.80	0.008
ApoB 10108	−0.099	2.64	0.01
Atenolol treatment			
SBP change	0.25	1.07	0.29
DBP change	0.26	0.86	0.39
ADRA2A 1817 GG	−0.15	2.88	0.006

Genotypes with a *P* value < 0.10 in univariate analyses (see Table 3) were included in the models. Only genotypes with a *P* value < 0.01 are reported in the table above. The change in LVMI was calculated as a relative change from baseline. The relative changes in systolic and diastolic blood pressure were forced into the model. A negative regression coefficient corresponds to a reduction in LVMI. SBP, systolic blood pressure; DBP, diastolic blood pressure; AGT, angiotensinogen; ApoB, apolipoprotein B; ADRA2A, α_{2A} adrenoreceptor.

these genotypes included in the multiple regression model, the change in blood pressure was no longer a significant independent predictor of the change in LV mass index.

The angiotensinogen 1198C allele (corresponding to the AGT 235T variant) and the angiotensinogen 1218A (-6A) allele are in linkage disequilibrium ($P < 0.0001$, χ^2 test).

Discussion

This study shows that SNP profiles may predict the change in left ventricular (LV) mass in response to antihypertensive treatment, in a drug-specific manner. The angiotensinogen M235T and the apolipoprotein B G10108A polymorphism predicted the change in LV mass in response to irbesartan, while the α_{2A} adrenoreceptor A1817G gene polymorphism predicted the response for those treated with atenolol. Interestingly, the predictive power of these SNPs was greater than that of the magnitude of blood pressure reduction in predicting the change in LV mass.

The angiotensinogen (AGT) 235T variant, corresponding to a methionine to threonine substitution at amino acid residue 235 in the angiotensinogen molecule, has been shown to be a marker of an increased risk of hypertension [22–26]. However, the AGT M235T polymorphism is located in the coding region of the angiotensinogen gene and is therefore not thought to influence gene expression. The relationship with angiotensinogen levels and hypertension may be explained by linkage disequilibrium of this polymorphism with genetic variants in the promoter region, e.g. A-6G, leading to altered expressional levels [23,24,26–29].

The prevalence of LV hypertrophy has also been studied in relation to angiotensinogen polymorphisms, with

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somewhat conflicting results [30–34]. It appears likely that the AGT 235T variant is a marker of increased risk for greater LV mass. We have previously reported that the AGT T174M was a more powerful predictor of the change of LV mass, as compared to the M235T variant, in response to the AT_1 receptor antagonist irbesartan [16]. However, as these polymorphisms are in close linkage disequilibrium, the addition of more patients in the present study favored the AGT M235T variant as predictive of the change in LV mass. However, we do believe that both the previous findings [16] and the current results suggest that the angiotensinogen gene plays a role in the development and maintenance of LV hypertrophy. In addition, these results imply that it is individuals with the genotype related to a higher cardiovascular risk, in this case the AGT 235T variant, that benefit most from treatment.

In previous pharmacogenetic studies, we showed that antihypertensive patients treated with atenolol, and not irbesartan, showed an angiotensinogen genotype (M235T and G-6A)-related blood pressure response [18]. These results may appear inconsistent with our current findings. However, they may imply that the blood pressure response to antihypertensive treatment is governed by genetic loci separate from those that influence the treatment-induced change in LV mass. This line of reasoning is supported by the identification of quantitative trait loci linked to cardiac mass independently of blood pressure loci [35,36], and that common genetic or other common familial factors do not appear to be an important source of correlation between blood pressure and LV mass in first-degree relatives [37].

Apolipoprotein B (apoB) is a glycoprotein involved in lipoprotein metabolism and the maintenance of cholesterol homeostasis, through its function as a structural component of lipoproteins and as a ligand for the low-density lipoprotein (LDL) receptor. ApoB gene polymorphisms are associated with cholesterol, LDL, apoB, and triglyceride levels, and the risk for coronary artery disease [38]. Furthermore, dyslipidemia and an unfavorable fatty acid profile can predict the development of LV hypertrophy in middle-aged men [39]. We present results demonstrating that the apoB G101081A gene polymorphism (corresponding to the change from arginine to glutamine at amino acid residue 3611) is related to the change in LV mass index in response to irbesartan, further supporting a connection between lipids and LV hypertrophy. Despite lack of unambiguous evidence on this gene polymorphism's functional relevance and its relationship with lipid levels, the amino acid substitution at residue 3611 is within the putative receptor binding domain of apoB [40–42], portraying a possible effect on protein function [43].

An increased cardiac sympathetic nerve activation and noradrenaline release, caused by a selective increase in central sympathetic outflow to the heart, is present in hypertensive subjects with an increased LV mass [44]. Thus, noradrenaline released from cardiac sympathetic nerves acting on α_1 adrenoreceptors (AR) is likely to increase LV mass and is under the control of prejunctional α_{2A} AR-mediated feedback inhibition [45]. Clonodone, a centrally acting sympathoinhibitory drug acting via the stimulation of α_{2A} AR in the brainstem, normalizes cardiac function, ventricular stiffness and prevents LV structural remodeling in a hypertensive rat model [46], and reduces LV hypertrophy in humans [47]. Our results show that the α_{2A} AR A1817G polymorphism is related to the change in LV mass in response to atenolol treatment. This appears to support the role of the α_{2A} AR in the development of LV hypertrophy.

The genotypes ACE 10578 AG, the AGT 1237 GG, and the CETP 1336 AG were associated with a remarkably pronounced change in LV mass in response to irbesartan (a reduction of 66 g/m^2). Interestingly, these three genotypes were all present in the same individual subject, exemplifying the usage of genotype analysis in identifying extreme responders.

An important limitation of this study is the small sample size. The results should therefore be viewed as preliminary until confirmed in larger prospective studies. Secondly, it is reasonable to assume that a large number of gene polymorphisms are involved in the response to (antihypertensive) pharmacotherapy, rendering the microarray technology suitable. However, a microarray-based approach will invariably lead to multiple comparisons. We have therefore used a lower P value ($P < 0.01$) in order to reduce the number of false-positive results.

Thirdly, 12 weeks of antihypertensive treatment may be viewed as too short to assess adequately the change in LV mass in response to treatment. Therefore, the conclusions drawn from this study may only apply to the early phase of LV hypertrophy regression. Despite these limitations, we found that SNPs in the angiotensinogen gene and the apoB gene were predictive of the response, measured as the change in LV mass index, to the AT_1 receptor antagonist irbesartan; and a SNP in the α_2 adrenoreceptor was predictive of the response for those treated with the beta-blocker atenolol.

In conclusion, specific SNPs in the angiotensinogen, the apoB and the α_{2A} adrenoreceptor gene are related to the change in left ventricular mass index in response to antihypertensive treatment in a drug-specific manner. Only part of the change in LV mass index in response to antihypertensive treatment can be pre-

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dicted by the change in blood pressure, but the results suggest that the predictive power of specific genotypes is more important when both these factors are compared. This study exemplifies a strategy, in which panels of SNPs may be identified which are predictive of the response to treatment.

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