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Association of a $G^{994} \rightarrow T$ ($Val^{279} \rightarrow Phe$) polymorphism of the plasma platelet-activating factor acetylhydrolase gene with myocardial damage in Japanese patients with nonfamilial hypertrophic cardiomyopathy

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Abstract Plasma platelet-activating factor acetylhydrolase (PAF-AH) acts as a key defense against oxidative stress by hydrolyzing PAF and oxidized phospholipids. Deficiency of the activity of this enzyme may thus potentially result in predisposition to myocardial damage. The possible role of the G^{994} (*V* allele) $\rightarrow$ T (*F* allele) polymorphism of the *PAF-AH* gene in modulating cardiac function was investigated in 142 Japanese subjects with nonfamilial hypertrophic cardiomyopathy (HCM). Logistic regression analysis adjusted for age, sex, height, and body weight revealed that the frequency of the *F* allele was significantly higher in HCM patients than in 284 healthy controls. Echocardiographic examination revealed that left ventricular (LV) end-diastolic and end-systolic dimensions were significantly greater in HCM patients with the *FF* genotype than in those with the *VV* genotype. Cardiac catheterization revealed that LV end-diastolic pressure was significantly higher, whereas the LV ejection fraction was significantly smaller, for HCM patients with the *F* allele than for those with the *VV* genotype. Interstitial fibrosis was significantly more severe in HCM subjects with the *FF* genotype than in those with the *VV* genotype. These results suggest that the $G^{994} \rightarrow T$ ($Val^{279} \rightarrow$ Phe) polymorphism in the plasma *PAF-AH* gene may exacerbate cardiac damage in Japanese individuals with nonfamilial HCM, although this polymorphism is unlikely to be a causative factor for this condition.

Key words Platelet-activating factor · PAF acetylhydrolase · Polymorphism · Hypertrophic cardiomyopathy · Cardiac function · Oxidized phospholipids

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Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular (LV) hypertrophy with a predominant involvement of the interventricular septum (IVS), and is distinguished pathologically by disarray of the myocytes and myofibrils (Marian and Roberts 1995; Schwartz et al. 1995). Familial HCM results from mutations in various genes, including those encoding the β-myosin heavy chain (Geisterfer-Lowrance et al. 1990; Watkins et al. 1992), α-tropomyosin (Thierfelder et al. 1994), cardiac troponin T (Thierfelder et al. 1994), myosin binding protein–C (Bonne et al. 1995; Watkins et al. 1995), cardiac troponin I (Kimura et al. 1997), and essential and regulatory light chains of myosin (Poetter et al. 1996). However, genetic contributions to nonfamilial HCM, which is responsible for about half of all cases of HCM (Schwartz et al. 1995), remain to be characterized. Given that the myocardial response to stimuli is modulated by a variety of genes that interact with each other, the phenotypic expression of HCM may be influenced by additional modifying genes that affect cardiovascular function (Lechin et al. 1995; Marian and Roberts 1995; Brugada et al. 1997).

Platelet-activating factor (PAF) is a proinflammatory phospholipid that stimulates platelets, leukocytes, macrophages, vascular smooth muscle cells, and cardiomyocytes as a result of its binding to a specific cell-surface receptor (Honda et al. 1991; Sugimoto et al. 1992; Zimmerman et al. 1992). PAF exerts pronounced vascular and myocardial effects (Kenzora et al. 1984; Levi et al. 1984; Laurindo et al. 1989). Thus, the intravenous injection of PAF increases both systemic and pulmonary vascular resistance and markedly reduces cardiac output (Kenzora et al. 1984). PAF induces hypotension as a result of pulmonary vasoconstriction and consequent acute right ventricular failure, decreased LV filling, and reduced cardiac output (Laurindo et al. 1989). PAF also reduces myocardial function by inducing constriction of coronary arteries. Administration of PAF either to isolated heart preparations or in vivo induces regional or global myocardial ischemia and

myocardial dysfunction (Levi et al. 1984). In addition, studies with cardiac muscle strips and isolated perfused hearts have revealed a direct negative inotropic effect of PAF that is independent of preload, afterload, coronary flow, or autonomic tone (Kenzora et al. 1984; Levi et al. 1984).

One of the key processes in impairment of cardiac function may be oxidative damage to the myocardium. Mice that lack intramitochondrial manganese superoxide dismutase activity exhibit abnormalities of the myocardium that resemble characteristics of dilated cardiomyopathy (Li et al. 1995). Oxygen radicals have been implicated in the pathogenesis of ischemic and postischemic reperfusion injury in the heart (McCord 1985). Reactive oxygen species oxidize polyunsaturated fatty acyl chains in membrane phospholipids (Patel et al. 1992), and the resulting oxidized phospholipids have the potential to affect the myocardium by acting as PAF receptors (Smiley et al. 1991; Sugimoto et al. 1992; Alloatti et al. 1994). Morgan et al. (1999) recently showed that intravenous administration of recombinant plasma PAF acetylhydrolase (PAF-AH), which hydrolyzes PAF and oxidized phospholipids to inactive metabolites (Stafforini et al. 1987; Stremler et al. 1991), reduces myocardial injury induced by ischemia-reperfusion in rabbits. Thus, impairment of defense mechanisms against PAF and oxidized phospholipids may confer susceptibility to myocardial damage.

A $G^{994} \rightarrow T$ polymorphism in exon 9 of the plasma *PAF-AH* (*PLA2G7*) gene, which encodes the catalytic domain of the enzyme, has been identified in Japanese families that show a deficiency of plasma PAF-AH activity (Stafforini et al. 1996). This nucleotide change results in a $Val^{279} \rightarrow Phe$ (V279F) substitution in the mature protein and in the loss of catalytic activity. We have previously shown that this polymophism is a genetic risk factor for myocardial infarction in Japanese men (Yamada et al. 1998). We have also demonstrated that the $G^{994} \rightarrow T$ polymorphism may contribute to genetic susceptibility to or progression of dilated cardiomyopathy in Japanese (Ichihara et al. 1998).

We have now investigated whether the $G^{994} \rightarrow T$ polymorphism of the plasma *PAF-AH* gene modifies cardiac function in Japanese subjects with nonfamilial HCM.

Subjects and methods

Study population

The study population consisted of 142 Japanese patients with nonfamilial HCM and 284 healthy individuals, all of whom had visited 14 participating hospitals between July 1994 and December 2000. Informed consent was obtained from each subject. The diagnosis of HCM was based on family and patient history, physical examination, electrocardiography, chest X-ray, and echocardiography. All patients were free of hypertension, coronary artery disease, valvular heart disease, congenital malformations of the heart and vessels, and intrinsic pulmonary, renal, or metabolic diseases; patients with secondary HCM were excluded from the study. Healthy individuals were selected as a normal control group from persons who visited the participating hospitals for an annual medical checkup or for various symptoms and who were found not to exhibit any serious disorders.

Assay for plasma PAF-AH activity

Venous blood was collected into a tube containing ethylenediamine tetraacetate (EDTA) (disodium salt, 50 mM) in the early morning after the patient had fasted overnight and was centrifuged at 1600*g* for 15 min at 4°C. Plasma samples were stored at −30°C. The activity of PAF-AH in plasma was measured for 247 individuals (186 controls and 61 HCM patients) as previously described (Stafforini et al. 1987).

Plasma PAF-AH genotyping

The genotype of the plasma *PAF-AH* gene was determined with an allele-specific polymerase chain reaction (PCR) as previously described (Stafforini et al. 1996; Yamada et al. 1998).

Echocardiographic examination

Patients with HCM were subjected to echocardiographic examination. The LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), as well as the end-diastolic thickness of the IVS and the LV posterior wall (LVPW), were determined by two-dimensional echocardiography. The maximal thickness of the LV wall was measured at end-diastole in the region of greatest hypertrophy.

Cardiac catheterization

Cardiac catheterization was performed in 84 subjects with HCM. A 6F pigtail angiographic catheter tipped with a high-fidelity micromanometer (model SPC-464D; Millar Instruments, Houston, TX, USA) was advanced into the left ventricle through the right brachial artery for measurement of LV pressure, including LV end-diastolic pressure (LVEDP), the maximum positive derivative of LV pressure [(+)LV dP/dt_{max}], the minimum negative derivative of LV pressure [(−)LV dP/dt_{min}], and the pressure half-time ($T_{1/2}$) (Izawa et al. 1997; Inagaki et al. 1999). A 20-gauge catheter was placed in the left brachial artery for measurement of arterial pressure. A 7F triple-lumen thermistor Swan-Ganz catheter was positioned in the pulmonary artery through the right brachial vein. Cardiac output was measured by the thermodilution method. Coronary angiography and left ventriculography were performed: LV end-systolic and end-diastolic volumes were determined by biplane ventriculography, and LV ejection fraction (LVEF) was calculated by the area-length method (Dodge et al. 1966).

Endomyocardial tissue was obtained from the right side of the IVS by right ventricular catheterization for histological examination. The histological findings, including hypertrophy, disarray, and degeneration of cardiac myocytes as well as interstitial fibrosis, were graded by pathologists who were not aware of the patient's *PAF-AH* genotype according to the following scale: 0, none; 1, mild; 2, moderate; and 3, severe.

Statistical analysis

Data are presented as means ± SD. They were compared between two groups by the Mann-Whitney *U* test. Comparison of data among plasma *PAF-AH* genotypes was performed by the Kruskal-Wallis test and Scheffe's test. Qualitative data were compared by the chi-square test. Allele frequencies were estimated by the gene counting method, and the significance of deviation from Hardy-Weinberg equilibrium was analyzed by the chi-square test. We performed multivariable logistic regression analysis to adjust factors, with HCM as the dependent variable and the independent variables age, sex, height, body weight, and plasma *PAF-AH* genotype. Plasma *PAF-AH* genotype was assessed according to dominant ($0 = VV, 1 = VF = FF$), recessive ($0 = VV = VF, 1 = FF$), and additive [$(0, 0) = VV$, $(1, 0) = VF$, $(0, 1) = FF$] genetic models. The odds ratio and 95% confidence interval (CI) were calculated. A P value of <0.05 was considered statistically significant.

Results

Allele-specific PCR analysis accurately detected the $G^{994} \rightarrow T$ polymorphism in the plasma *PAF-AH* gene (Ichihara et al. 1998; Yamada et al. 1998). The frequencies of the *VV*, *VF*, and *FF* genotypes were 72.9, 22.9, and 4.2%, respectively, among the 284 control individuals, and 54.2, 38.0, and 7.7%, respectively, among the 142 nonfamilial HCM patients (Table 1). The distribution of genotypes among controls as well as among subjects with HCM was in Hardy-Weinberg equilibrium. Multivariable logistic regression analysis adjusted for age, sex, height, and body weight revealed that the frequency of the *F* allele was significantly higher in patients with HCM than in healthy controls in analyses assuming a dominant or additive effect of the *F* allele (Table 1).

Plasma PAF-AH activity was significantly associated with genotype in both control and patient groups (Table 2). For both controls and subjects with HCM, the plasma activity was significantly greater in individuals with the *VV* genotype than in those with the *VF* genotype or the *FF* genotype. As expected, no activity was detected in individuals with the *FF* genotype. Plasma PAF-AH activity did not differ between controls and HCM patients of the same genotype.

Echocardiographic examination revealed that LVEDD and LVESD were significantly greater in HCM patients with the *FF* genotype than in those with the *VV* genotype (Table 3). There were no significant differences in end-diastolic thickness of the IVS or LVPW among *PAF-AH* genotypes.

Cardiac catheterization revealed that systolic pulmonary artery pressure, pulmonary artery wedge pressure, LVEDP, (+)LV dP/dt_{max}, and $T_{1/2}$ were significantly greater in HCM patients with the *VF* genotype or the *FF* genotype than in patients with the *VV* genotype (Table 4). LVEF was significantly smaller in HCM patients with the *F* allele than in those with the *VV* genotype (Table 4); seven HCM patients who showed an LVEF of <50% all possessed the *F* allele (data not shown).

Histological examination revealed that the severity of hypertrophy, disarray, and degeneration of cardiac myocytes did not differ among *PAF-AH* genotypes for HCM patients (data not shown). Interstitial fibrosis was significantly more developed in HCM subjects with the *FF* genotype (grade, 1.7 ± 0.5) than in those with the *VV* genotype (grade, 0.9 ± 0.7; $P < 0.05$, Kruskal-Wallis test and Scheffe's test).

Table 1. Distribution of plasma *PAF-AH* genotypes among healthy controls and patients with nonfamilial HCM

	Controls	HCM patients
No. of subjects	284	142
Sex (male/female)	221/63	114/28
Age (years)	55.3 ± 8.2	55.9 ± 10.3
Height (cm)	163.4 ± 8.2	162.9 ± 7.7
Body weight (kg)	61.4 ± 9.7	64.7 ± 10.7*
PAF-AH genotype		
VV	207 (72.9%)	77 (54.2%)
VF	65 (22.9%)	54 (38.0%)
FF	12 (4.2%)	11 (7.7%)
Allele frequency (*V*/*F*)	0.84/0.16	0.73/0.27
Dominant effect		
P (*VF* + *FF* versus *VV*)	0.0007	
Odds ratio (95% CI)	2.3 (1.4–3.7)	
Recessive effect		
P (*FF* versus *VV* + *VF*)	0.193	
Additive effect		
P (*VF* versus *VV*, *FF* versus *VV*)	0.002, 0.04	
Odds ratio (95% CI)	2.2 (1.4–3.7), 2.4 (0.9–6.4)	

PAF-AH, platelet-activating factor acetylhydrolase; HCM, hypertrophic cardiomyopathy
* $P = 0.004$ versus controls (Mann-Whitney *U* test)

Table 2. Plasma PAF-AH activity in healthy controls and patients with nonfamilial HCM according to plasma *PAF-AH* genotype

	Plasma PAF-AH activity (nmol/min per ml)		
	VV	*VF*	*FF*
Controls	33.6 ± 7.4** ($n = 128$)	17.4 ± 5.6*** ($n = 46$)	0.1 ± 0.1* ($n = 12$)
HCM patients	34.3 ± 8.5** ($n = 36$)	18.4 ± 7.2*** ($n = 19$)	0.0 ± 0.0* ($n = 6$)

* $P < 0.001$ (Krukcal-Wallis test); ** $P < 0.0001$ versus *VF* or *FF*; *** $P < 0.0001$ versus *FF* (Scheffe's test)

Discussion

Several studies of familial HCM have shown that the extent of hypertrophy varies significantly among affected individuals, among members of the same family with the mutation as well as among different families, suggesting that additional genetic and environmental factors contribute to the progression of hypertrophy (Lechin et al. 1995; Brugada et al. 1997). Polymorphisms in the angiotensin-converting enzyme and endothelin-1 genes modify the phenotypic expression of hypertrophy in patients with familial HCM, indicating that gene-to-gene interactions may account for the variable clinical manifestations of this condition (Lechin et al. 1995; Brugada et al. 1997). Although genetic contributions to nonfamilial HCM have not been identified, the disease phenotype also may be attributable to interaction of the responsible gene with other genetic and environmental influences.

We have now detected an association of the $G^{994} \rightarrow T$ polymorphism in the plasma *PAF-AH* gene, which results in a loss of catalytic activity of the encoded enzyme, with the prevalence of nonfamilial HCM in Japanese. Because the plasma activity of the enzyme is determined by genotype, low or lack of activity may affect the genetic susceptibility to HCM, at least in Japanese. In addition, cardiac function in subjects with HCM was related to *PAF-AH* genotype. Echocardiographic examination revealed that LVEDD and LVESD in patients with HCM increased according to the rank order of genotypes $VV < VF < FF$, with significant differences apparent between individuals with the *VV* genotype and those with the *FF* genotype. Cardiac catheterization revealed that both LVEDP and $T_{1/2}$ were increased and LVEF was decreased in HCM patients with the *F* allele compared with the corresponding values for those with the *VV* genotype. These results suggest that the $G^{994} \rightarrow T$ polymorphism of the plasma *PAF-AH* gene may contribute to impairment of LV function in individuals with HCM. Furthermore, the seven HCM patients with an LVEF of <50% were all individuals with the *F* allele. The association of the plasma *PAF-AH* gene polymorphism with impaired cardiac function is also supported by the observation that interstitial fibrosis was more developed in HCM subjects with the *FF* genotype than in those with the *VV* genotype.

Prolonged exposure of the myocardium to PAF and oxidized phospholipids may result in myocardial damage (Kenzora et al. 1984; Levi et al. 1984; Laurindo et al. 1989; Sugimoto et al. 1992; Zimmerman et al. 1992; Alloatti et al. 1994). It is thus possible that the $G^{994} \rightarrow T$ polymorphism of

Table 3. Echocardiographic characteristics of patients with nonfamilial HCM according to plasma PAF-AH genotype

	Genotype of HCM patients		
	VV	*VF*	*FF*
No. of subjects	77	54	11
Sex (male/female)	59/18	46/8	9/2
Age (years)	56.6 ± 10.5	55.9 ± 10.0	51.5 ± 10.2
Height (cm)	162.1 ± 7.6	163.9 ± 7.7	164.4 ± 9.1
Body weight (kg)	63.5 ± 10.4	65.8 ± 9.9	67.7 ± 15.6
Echocardiography			
LVEDD (mm)	45.9 ± 6.3	47.8 ± 5.5	51.1 ± 7.2*
LVESD (mm)	27.7 ± 5.7	30.4 ± 6.0	34.1 ± 8.5*
IVS (mm)	17.0 ± 4.5	16.8 ± 3.7	18.8 ± 4.5
LVPW (mm)	11.9 ± 2.6	11.7 ± 2.3	13.4 ± 3.4

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVS, interventricular septum; LVPW, left ventricular posterior wall

* $P < 0.05$ (Kruskal-Wallis test); $P < 0.05$ versus *VV* (Scheffe's test)

Table 4. Hemodynamic characteristics of patients with nonfamilial HCM according to plasma *PAF-AH* genotype

	Genotype of HCM patients		
	VV	*VF*	*FF*
No. of subjects	44	33	7
Sex (male/female)	39/5	29/4	6/1
Age (years)	53.0 ± 9.9	54.1 ± 9.3	52.1 ± 7.7
Height (cm)	164.7 ± 6.0	165.2 ± 6.1	164.7 ± 7.9
Body weight (kg)	65.7 ± 8.8	66.1 ± 8.8	70.7 ± 16.9
Cardiac catheterization			
Systolic BAP (mmHg)	134.1 ± 21.3	136.6 ± 23.3	142.0 ± 10.6
Diastolic BAP (mmHg)	77.0 ± 13.2	75.6 ± 12.4	79.0 ± 7.0
Systolic PAP (mmHg)	22.1 ± 4.8	23.9 ± 6.3	29.9 ± 3.8*******|
Diastolic PAP (mmHg)	9.3 ± 3.8	9.8 ± 3.5	12.1 ± 3.7
PAWP (mmHg)	9.0 ± 3.7	11.2 ± 3.6*****	10.0 ± 2.6*
Cardiac output (l/min)	4.9 ± 1.1	4.7 ± 0.8	4.8 ± 0.9
LVEF (%)	73.5 ± 8.2	66.0 ± 13.3*****	60.3 ± 10.6******|
LVEDP (mmHg)	10.9 ± 4.5	16.4 ± 5.5****	18.9 ± 5.6*****|
(+)LV dP/dt_{max} (mmHg/s)	1737 ± 341	2024 ± 371*****	1783 ± 563**
(−)LV dP/dt_{min} (mmHg/s)	−1694 ± 436	−1771 ± 446	−1200 ± 173
$T_{1/2}$ (ms)	39.6 ± 7.1	40.3 ± 5.8	48.0 ± 5.0******|

BAP, brachial artery pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure

* $P < 0.01$; ** $P < 0.05$ (Kruskal-Wallis test); *** $P < 0.05$ versus *VF*; **** $P < 0.01$ versus *VV*; ***** $P < 0.05$ versus *VV* (Scheffe's test)

the plasma *PAF-AH* gene contributes to myocardial damage as a result of the reduced defense against PAF and oxidized phospholipids. However, it is unlikely that this polymorphism is a causative factor for HCM, given that, in the present study, 54% of HCM patients exhibited the normal genotype. The $G^{994} \rightarrow T$ polymorphism significantly increased cardiac mass, as evidenced by echocardiography, but it did not affect the extent of myofibrillar disarray, a hallmark of HCM, as revealed by histological examination. These observations suggest that the increased cardiac mass associated with the $G^{994} \rightarrow T$ polymorphism represents a physiological response to myocardial damage induced by PAF and oxidized phospholipids. We previously showed that LVEDD, LVESD, and LV mass in patients with dilated cardiomyopathy with the *VF* or *FF* genotypes were significantly greater than those in patients with the *VV* genotype (Ichihara et al. 1998). The effect of the $G^{994} \rightarrow T$ polymorphism on myocardial damage therefore may not be specific for nonfamilial HCM but rather may represent a general phenomenon.

The distribution of plasma *PAF-AH* genotypes and allele frequencies among control individuals in the present study (*VV* 73%, *VF* 23%, *VV* 4%; *V* 84%, *F* 16%) did not differ from those observed in Tokyo, Tochigi Prefecture, and Gunma Prefecture (*VV* 67%, *VF* 30%, *FF* 3%; *V* 82%, *F* 18%) (Stafforini et al. 1999), in Aomori Prefecture (*VV* 71%, *VF* 27%, *FF* 2%; *V* 84%, *F* 16%) (Yoshida et al. 1998), or in our previous large study population in Aichi and Aomori Prefectures (*VV* 70%, *VF* 27%, *FF* 3%; *V* 83%, *F* 17%) (Yamada et al. 2000). However, the genotype distribution and allele frequencies in the present study differed significantly from those described by Satoh et al. (1999) for Tokyo (*VV* 62%, *VF* 32%, *FF* 6%, $P = 0.04$; *V* 78%, *F* 22%, $P = 0.02$, chi-square test), although the reason for this difference remains unclear.

In conclusion, the $G^{994} \rightarrow T$ (V279F) polymorphism in the plasma *PAF-AH* gene may act as a modulating factor for myocardial damage in Japanese individuals with nonfamilal HCM, although this polymorphism is unlikely to be a causative factor for this disease.

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