Identification of a polymorphism of *UCP3* associated with recurrent in-stent restenosis of coronary arteries

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Received April 30, 2007; Accepted June 8, 2007

Abstract. The purpose of the present study was to identify gene polymorphisms that confer susceptibility to recurrent restenosis after bare-metal stenting of coronary arteries, and thereby to assess the genetic risk for this condition. The study population comprised 527 unrelated Japanese individuals, including 28 subjects who developed in-stent restenosis two or more times and 499 subjects without restenosis. The genotypes for 142 polymorphisms of 121 candidate genes were determined with a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology. Eleven polymorphisms were related ($P<0.05$) to the prevalence of recurrent in-stent restenosis as determined by the Chi-square test. Multivariable logistic regression analysis with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia revealed that the -55C→T polymorphism of the uncoupling protein 3 gene (*UCP3*) was significantly ($P=0.0006$ in a recessive model) associated with the prevalence of recurrent in-stent restenosis, with the *T* allele representing a risk factor for this condition. A stepwise forward selection procedure showed that the *UCP3* genotype significantly ($P=0.0014$, recessive model) affected the prevalence of recurrent in-stent restenosis. Determination of the genotype for *UCP3* may thus contribute to assessment of the genetic risk for recurrent in-stent restenosis.

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Key words: polymorphism, genetics, coronary heart disease, in-stent restenosis, uncoupling protein 3

Introduction

Despite recent advances in percutaneous coronary intervention, in-stent restenosis remains an important problem in this therapeutic strategy. Although a substantial reduction in the rate of restenosis has been achieved with the use of drug-eluting stents (1,2), this condition remains difficult to manage in some patients and may necessitate repeated coronary interventions (3). The ability to stratify patients according to risk for in-stent restenosis would therefore be clinically beneficial.

Many recent studies have demonstrated a genetic component to in-stent restenosis (4). Indeed, conventional risk factors alone cannot account for the overall risk for this condition. Association studies have identified several candidate genes that may predispose to in-stent restenosis (5-7). However, the genes that confer susceptibility to this condition remain to be identified definitively.

We have now performed an association study for 142 candidate gene polymorphisms and recurrent in-stent restenosis after bare-metal stenting of coronary arteries in 527 Japanese individuals. The purpose of our study was to identify genetic polymorphisms that confer susceptibility to recurrent restenosis after coronary stenting in order to facilitate risk stratification for this condition.

Materials and methods

Study population. The study population comprised 527 unrelated Japanese individuals (406 men, 121 women) who underwent successful bare-metal stenting one or more times in previously untreated coronary arteries at the participating hospitals (Gifu Prefectural Tajimi Hospital and Gifu Prefectural General Medical Center) between October 2002 and March 2005. The coronary lesions were examined by coronary angiography 6 months after stenting. Quantitative angiographic measurements were performed on end-diastolic frames. In-stent restenosis was defined as narrowing at follow-up of >50% of the minimal lumen diameter at the site of stenting. Subjects who developed restenosis two or more

Table I. Baseline characteristics of the study subjects (n=527).

Characteristic	No restenosis (n=499)	Recurrent in-stent restenosis (n=28)	P
Age (years)	66.2±10.2	68.1±8.1	0.250
Sex (male/female)	388/111	18/10	0.120
BMI (kg/m^2)	23.8±3.2	23.8±2.8	0.980
Current or former smoker (%)	49.3	50.0	0.940
Hypertension (%)	71.9	82.1	0.220
Diabetes mellitus (%)	47.5	82.1	<0.001
Hypercholesterolemia (%)	62.9	67.9	0.600
Acute coronary syndrome (%)	30.5	42.9	0.180
Coronary lesions			0.450
Right coronary artery [no. (%)]	259 (38.5)	30 (44.1)	
Left anterior descending artery [no. (%)]	263 (39.1)	20 (29.4)	
Left circumflex artery [no. (%)]	145 (21.5)	17 (25.0)	
Left main coronary artery [no. (%)]	6 (0.9)	1 (1.5)	
ACC/AHA lesion type B2 or C (%)	34.7	64.3	<0.010

Quantitative data are the means ± SD. Smoker, ≥10 cigarettes daily; hypertension, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (or both), or taking antihypertensive medication; diabetes mellitus, fasting plasma glucose concentration ≥126 mg/dl or hemoglobin A_{1c} ≥6.5% (or both), or taking antidiabetes medication; hypercholesterolemia, serum total cholesterol ≥220 mg/dl or taking lipid-lowering medication. ACC/AHA, American College of Cardiology/American Heart Association.

times at any coronary arterial lesion were determined to have recurrent restenosis. Binary restenosis or other restenosis unrelated to implantation of the coronary stent was excluded. A total of 499 subjects (388 men, 111 women) exhibited no restenosis after coronary stenting, and 28 subjects (18 men, 10 women) manifested restenosis two or more times after repeat stenting. Subjects with subacute stent thrombosis were excluded from the study.

The study protocol complied with the Declaration of Helsinki and was approved by the Committees on the Ethics of Human Research of Gifu Prefectural Tajimi Hospital and Gifu Prefectural General Medical Center, Gifu International Institute of Biotechnology, and Mie University School of Medicine. Written informed consent was obtained from each participant.

Selection and genotyping of polymorphisms. With the use of public databases, we selected 142 polymorphisms of 121 candidate genes that might be expected to influence restenosis (5). Genotypes of the 142 polymorphisms were determined at G&G Science (Fukushima, Japan) by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with analysis by suspension array technology (Luminex 100 flow cytometer; Luminex, Austin, TX, USA). Detailed methodology for genotyping was described previously (8).

Statistical analysis. Clinical data were compared between subjects with recurrent in-stent restenosis and those without restenosis by the unpaired Student's t-test. Data for lipid profiles were compared among three groups by one-way analysis of variance and the Dunnett's *post hoc* test, and between two groups by the unpaired Student's t-test. Qualitative data were compared by the Chi-square test. Allele frequencies were estimated by the gene counting method, and the Chi-square test was used to identify departure from Hardy-Weinberg equilibrium. The genotype distribution of each autosomal polymorphism was compared between subjects with recurrent in-stent restenosis and those without restenosis by the Chi-square test (3x2); for polymorphisms on the X chromosome, allele frequencies were compared by the Chi-square test (2x2). Polymorphisms related (P<0.05) to recurrent in-stent restenosis were further examined by multivariable logistic regression analysis with adjustment for covariates, with recurrent in-stent restenosis as a dependent variable and independent variables including age, sex (0 = woman, 1 = man), body mass index (BMI), smoking status (0 = nonsmoker, 1 = smoker), metabolic variables (0 = no history of hypertension, diabetes mellitus, or hypercholesterolemia; 1 = positive history), and the genotype of each polymorphism. Each genotype was assessed according to dominant, recessive, additive 1 (heterozygotes versus wild-type homozygotes), and additive 2 (variant homozygotes versus wild-type homozygotes) genetic models, and the P-value, odds ratio, and 95% confidence interval were calculated. We also performed a stepwise forward selection procedure to examine the effects of genotypes as well as of other covariates on recurrent in-stent restenosis. Given the multiple comparisons of genotypes with recurrent in-stent restenosis, we adopted a strict criterion, P<0.005, for statistical significance of association. For other clinical background data, a P-value of <0.05 was considered statistically significant. Statistical significance was examined by two-sided tests, and statistical analyses were performed with JMP version 5.1 software (SAS Institute, Cary, NC, USA).

Table II. Polymorphisms related (P<0.05) to recurrent in-stent restenosis as revealed by the Chi-square test and their genotype distributions (number of subjects).

Gene symbol	Polymorphism	No restenosis	Recurrent in-stent restenosis	P
UCP3	-55C→T			0.0033
	CC	241	8	
	CT	221	12	
	TT	37	8	
ADIPOQ	G→T in intron 2 (SNP-276)			0.0127
	GG	241	11	
	GT	203	17	
	TT	55	0	
ENG	C→G (Asp366His)			0.0127
	CC	3	1	
	CG	62	0	
	GG	434	27	
COL3A1	G→A (Ala698Thr)			0.0127
	GG	278	16	
	GA	192	6	
	AA	29	6	
MMP12	-82A→G			0.0223
	AA	482	24	
	AG	17	4	
	GG	0	0	
IL10	-592A→C			0.0245
	AA	235	17	
	AC	205	11	
	CC	59	0	
IL10	-819T→C			0.0250
	TT	236	17	
	TC	204	11	
	CC	59	0	
FGB	-455G→A			0.0313
	GG	381	16	
	GA	107	12	
	AA	11	0	
FGB	8059G→A (Arg448Lys)			0.0334
	GG	380	16	
	GA	108	12	
	AA	11	0	
THPO	5713A→G			0.0438
	AA	120	3	
	AG	250	12	
	GG	129	13	
HMOX1	-413T→A			0.0479
	TT	169	5	
	TA	221	4	
	AA	109	19	

Results

The characteristics of the 527 study subjects are shown in Table I. The prevalence of diabetes mellitus and of ACC/AHA lesion type B2 or C was greater in subjects with recurrent in-stent restenosis than in those without restenosis. Comparison of genotype distributions or allele frequencies by the Chi-square test revealed that 11 polymorphisms were related (P<0.05) to the prevalence of recurrent in-stent restenosis (Table II). The genotype distributions of these polymorphisms among subjects with recurrent in-stent restenosis and those without restenosis are also shown in Table II. The genotype distributions of these polymorphisms in subjects without restenosis were in Hardy-Weinberg equilibrium.

Multivariable logistic regression analysis with adjustment for age, sex, BMI, and the prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia revealed

Table III. Multivariable logistic regression analysis of polymorphisms related to recurrent in-stent restenosis with adjustment for age, sex, BMI, and the prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia.

Gene	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
UCP3	-55C→T	0.0462	2.4 (1.0-6.0)	**0.0006**	5.2 (1.9-13.0)	0.2846		**0.0006**	6.8 (2.3-20.7)
ADIPOQ	G→T in intron 2 (SNP-276)	0.0786		0.8680		0.1357		0.8723	
ENG	C→G (Asp366His)	0.1049		0.1413		0.8306		0.1224	
COL3A1	G→A (Ala698Thr)	0.8025		0.0059	4.2 (1.4-11.2)	0.1893		0.0256	3.3 (1.1-9.3)
MMP12	-82A→G	0.0315	3.9 (1.0-12.4)			0.0315	3.9 (1.0-12.4)		
IL10	-592A→C	0.0800		0.8659		0.2639		0.8628	
IL10	-819T→C	0.0806		0.8659		0.2658		0.8628	
FGB	-455G→A	0.0146	2.7 (1.2-6.2)	0.8774		0.0068	3.1 (ND)	0.8834	
FGB	8059G→A (Arg448Lys)	0.0155	2.7 (1.2-6.1)	0.8774		0.0073	3.1 (ND)	0.8833	
THPO	5713A→G	0.0824		0.0281	2.4 (1.1-5.3)	0.2289		0.0272	4.3 (1.3-19.6)
HMOX1	-413T→A	0.1183		0.4118		0.0634		0.7473	

OR, odds ratio; CI, confidence interval; ND, not determined. P-values <0.005 are shown in bold.

Table IV. Effects of genotypes and other characteristics on recurrent in-stent restenosis as determined by a stepwise forward selection procedure.

Variable	P	R^2
Diabetes mellitus	0.0002	0.0632
UCP3 (*TT* versus *CC* + *CT*)	0.0014	0.0469
COL3A1 (*AA* versus *GG* + *GA*)	0.0146	0.0273
THPO (*GG* versus *AA* + *AG*)	0.0158	0.0266
FGB-455G→A (*AA* + *GA* versus *GG*)	0.0281	0.0221

that the -55C→T polymorphism of the uncoupling protein 3 gene (*UCP3*) was significantly (P<0.005) associated with the prevalence of recurrent in-stent restenosis (recessive and additive 2 models), with the *T* allele representing a risk factor for this condition (Table III).

We performed a stepwise forward selection procedure to examine the effects (contribution rate, R^2) of genotypes for the polymorphisms identified by the Chi-square test as well as of age, sex, BMI, and the prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia on the prevalence of recurrent in-stent restenosis (Table IV). Diabetes mellitus and the *UCP3* genotype (recessive model) significantly (P<0.005) affected the prevalence of recurrent in-stent restenosis.

Finally, we examined the possible effect of the -55C→T polymorphism of *UCP3* on lipid profiles in all subjects. There were no differences in the serum concentrations of total, high density lipoprotein (HDL)-, or low density lipoprotein (LDL)-cholesterol or of triglyceride among or between *UCP3* genotypes (dominant or recessive model) (Table V).

Discussion

In-stent restenosis is characterized predominantly by neointimal proliferation through the stent strut, with inflammatory mechanisms being thought to play a pivotal role in this process (9). Statins and interleukin-10 have been shown to inhibit the inflammatory reaction and in-stent restenosis in animal studies (10,11). Genetic variation in inflammation-related genes is also thought to account, at least in part, for differences in the risk of inflammation-driven restenosis (12-14).

Although the development of in-stent restenosis is a major problem in percutaneous coronary intervention, it has proven difficult to stratify patients with regard to the risk of in-stent restenosis solely on the basis of conventional risk factors. Determination of genetic factors that might allow identification of individuals at high risk for in-stent restenosis is thus an important goal of clinical practice. We have now examined the possible relations of 142 polymorphisms in 121 candidate genes to recurrent in-stent restenosis in 527

Table V. Effect of *UCP3* genotype on lipid profiles.

Analyte	*CC*	*CT*	*TT*	P (dominant model)	P (recessive model)
Total cholesterol (mg/dl)	202.7±40.1	201.5±41.7	215.5±42.4	0.8183	0.1261
HDL-cholesterol (mg/dl)	46.4±13.9	45.6±13.3	48.0±13.2	0.7732	0.4691
LDL-cholesterol (mg/dl)	125.1±34.3	125.2±39.2	133.7±49.6	0.7310	0.3906
Triglyceride (mg/dl)	157.5±98.1	155.8±95.1	169.1±139.2	0.9632	0.6536

subjects. Our association study revealed that the -55C→T polymorphism of *UCP3* is significantly associated with the prevalence of recurrent in-stent restenosis in the Japanese population.

Uncoupling protein 3 (UCP3) is one of a family of molecules present in the inner mitochondrial membrane and is most abundant in skeletal muscle (15,16). Although the precise role of UCP3 remains to be elucidated, it functions to dissipate proton gradients and to uncouple respiration from oxidative phosphorylation, thus converting fuel to heat (17). *UCP3* is located on human chromosome 11q13, adjacent to *UCP2*. The *UCP2-UCP3* locus has been linked to variation in various quantitative traits associated with diabetes and insulin resistance in animals and humans (18). The *T* allele of the -55C→T polymorphism of *UCP3* has been associated with an increased BMI, an increased level of adiposity, or a greater waist-to-hip ratio (19,20). The *T* allele of this polymorphism has also been associated with a higher level of *UCP3* mRNA (21). Furthermore, in an association study of 1155 subjects including those with obesity and type 2 diabetes mellitus, the *T* allele of the -55C→T polymorphism of *UCP3* was found to be associated with an atherogenic lipid profile and a lower risk for type 2 diabetes (22); subjects with the *TT* genotype thus had significantly higher plasma concentrations of total cholesterol, LDL-cholesterol, and apolipoprotein B compared with those with other genotypes. In the present study, however, the serum concentrations of total, HDL-, or LDL-cholesterol or of triglyceride did not differ among *UCP3* genotypes. Although the reason for this difference between our results and those of the previous study (22) remains unclear, environmental factors such as diet might be responsible. We previously showed that the -55C→T polymorphism of *UCP3* was associated with myocardial infarction in individuals with hypercholesterolemia (23), with the *T* allele representing a risk factor for this condition. We have now shown that the -55C→T polymorphism of *UCP3* was associated with an increased risk for recurrent in-stent restenosis, and this association was not attributable to an effect of the polymorphism on lipid profiles. Although the underlying molecular mechanism remains to be elucidated, as far as we are aware this is the first demonstration of an association of this polymorphism of *UCP3* with recurrent in-stent restenosis.

There are several limitations of the present study. i) Given the small sample size, especially the low number of subjects with recurrent in-stent restenosis, it is not possible to avoid completely potential type II errors (false negatives). ii) Given the multiple comparisons of genotypes with recurrent in-stent restenosis, we adopted a strict criterion ($P<0.005$) for statistical significance of association. However, it is not possible to exclude completely potential type I errors (false positives). iii) It was not possible to evaluate the effects of different types of bare-metal stents on the association of genetic polymorphisms with recurrent in-stent restenosis. iv) It is also possible that the -55C→T polymorphism of *UCP3* is in linkage disequilibrium with polymorphisms of other nearby genes that are actually responsible for the association with recurrent in-stent restenosis.

In conclusion, our present results suggest that *UCP3* is a susceptibility locus for recurrent in-stent restenosis in Japanese individuals. Genotyping for this polymorphism may therefore facilitate assessment of the genetic risk for in-stent restenosis after coronary stenting.

Acknowledgements

This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (no. 15209021, to Y.Y), a grant from Gifu Prefectural Science and Technology Promotion Center (to Y.Y.), and a grant from St. Luke's Life Science Institute (to Y.Y.).

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