Original Article

Polymorphism of the C-Reactive Protein (CRP) Gene Is Related to Serum CRP Level and Arterial Pulse Wave Velocity in Healthy Elderly Japanese

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The objective of this study was to clarify relationships between the C-reactive protein (CRP) gene and both the serum level of CRP and arterial pulse wave velocity (PWV), using haplotype analysis of healthy elderly Japanese. Five single-nucleotide polymorphisms (SNPs) of the human CRP gene (rs1341665, rs3091244, rs1800947, rs1130864 and rs1205) were used to genotype 315 healthy elderly Japanese subjects (mean age, 77.9±4.1 years; male/female ratio, 0.96). Linkage disequilibrium was analyzed for the five SNPs. The frequency of each haplotype and diplotype was estimated using the expectation/maximization (EM) algorithm. There were statistically significant associations between the CRP level and two CRP genotypes; the *p* value for the T allele of rs3091244 (CT+AT+TT *vs.* CC+CA+AA) was 0.002 (95% confidential interval [CI], 2.1–24), and the *p* value for the T allele of rs1130864 (TT+TC *vs.* CC) was 0.002 (95% CI, 2.1–24). The only genotype that was significantly associated with arterial PWV was the C allele of rs1800947, with a *p* value of 0.039. The haplotype was constructed using rs1341665, rs3091244 and rs1800947, in that order. There was a significant association between the CRP level and the T-T-G haplotype, with a *p* value of 0.002 (95% CI, 2.1–24). There was a significant association between arterial PWV and the C-C-C haplotype, with a *p* value of 0.039. We concluded that rs3091244, rs1130864 and the T-T-G haplotype are genetic markers for elevated basal CRP levels. rs1800947 and the C-C-C haplotype appear to be susceptibility markers for atherosclerosis, but this requires confirmation. (*Hypertens Res* 2006; 29: 323–331)

***Key Words*: C-reactive protein, arterial pulse wave velocity, single-nucleotide polymorphism, haplotype, diplotype**

Introduction

Atherosclerosis, a major cause of cardio- and cerebrovascular diseases, is thought to involve inflammatory processes (*1*, *2*). C-reactive protein (CRP), an inflammatory marker, has been detected in atherosclerotic plaques (*3*), suggesting that CRP is directly involved in development of and/or vulnerability to atherosclerotic lesions (*4*). Thus, an elevated plasma CRP level may be an atherothrombotic biomarker that provides additive prognostic information not only for coronary heart disease (*5*, *6*) and/or cerebrovascular disease (*7*), but also for peripheral arterial disease associated with standard serum lipid profiles (*8*).

The human CRP gene is located at chromosome 1q21–1q23. It spans approximately 1,900 base pairs, and contains 2

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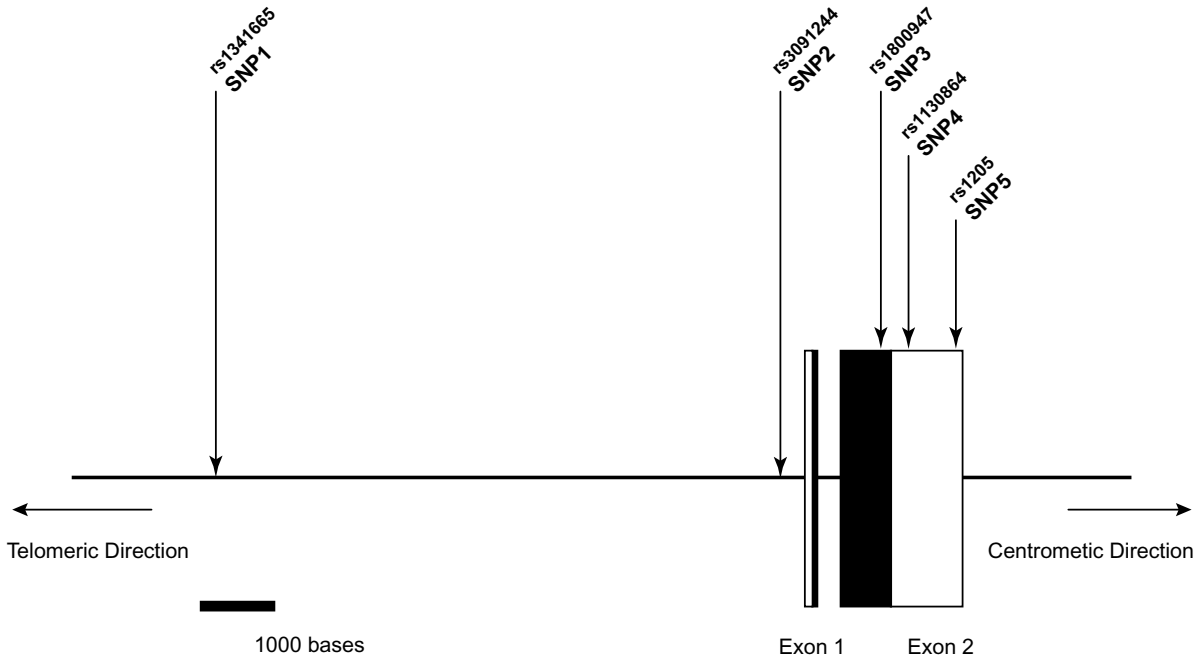

Fig. 1. *Structure of the human CRP gene. The gene consists of two exons separated by a single intron. The orientation of the gene in the centromeric and telomeric directions is marked by arrows. Boxes indicate exons, and lines indicate introns and intergenic regions. Filled boxes indicate coding regions. Arrows mark the locations of single-nucleotide polymorphisms. The length of the bar is equivalent to 1,000 base pairs.*

exons. There are 30 single nucleotide polymorphisms (SNPs) of the human CRP gene listed (accessed on September 30, 2005) in the National Center for Biotechnology Information (NCBI) SNP Database (http://www.ncbi.nlm.nih.gov/SNP). In the coding region, one silent mutation (rs1800947) has been detected, but no nonsense mutations have been detected (*9*). Some SNPs have been associated with elevated basal CRP levels, while others have been associated with reduced basal CRP levels (*10–13*). In case-control studies, the following SNPs have been detected in patients with the following diseases: rs2794521, type 2 diabetes mellitus (*14*); rs1205, systemic lupus erythematodes (SLE) and antinuclear autoantibody production (*10*); rs1130864, coronary heart disease after coronary artery bypass graft surgery (*11*).

Ankle brachial index and arterial pulse wave velocity (PWV) are clinical markers of atherosclerosis and risk predictors of cardio- and/or cerebrovascular diseases (*15*) and metabolic syndrome (*16*), and are obtainable using non-invasive methods (*17*, *18*). It has been reported that PWV is correlated with age and systolic blood pressure (*19*), and ankle brachial index and PWV are higher in subjects with elevated plasma CRP levels (*20–22*).

In the present study, we investigated the association between CRP gene polymorphism and both the serum CRP level and arterial PWV, using haplotype and diplotype analyses. The results should aid in the development of prophylactic treatments to extend the lifespan of healthy elderly individuals.

Methods

Subjects

The subjects were 315 essentially healthy elderly Japanese (mean age, 77.9±4.1 years). They were members of the New Elder Citizen Movement in Japan, the physical and psychosocial characteristics of which have been described elsewhere (*23*). The consulting doctors asked each subject about his or her medical history and symptoms. None of the subjects were taking any medication. Written informed consent was obtained from all subjects, and the study protocol was approved by the Human Studies Committee of Nihon University.

Genotyping

We selected five SNPs in the human CRP gene for use in the present genetic association study. All five SNPs had a minor allele frequency greater than 18% (*24*) or were established in previous studies (*10*, *11*), based on information in the NCBI SNP Database and the Applied Biosystems–Celera Discovery System (ABI-CDS, http://www.appliedbiosystems.com) Database. The five SNPs were designated SNP1–5 in order of their position within the CRP gene: rs1800947 (SNP3), in the intron 2 region; rs1341665 (SNP1) and rs3091244 (SNP2), in

Table 1. Characteristics of Study Participants

	Total	Male	Female
Number of subjects	315	154	161
Age (years)	77.9±4.1	78.3±4.5	77.7±3.7
BMI (kg/m^2)	22.6±2.9	22.8±2.7	22.4±3.0
sBP (mmHg)	135.9±16.4	135.7±15.3	136.2±17.4
dBP (mmHg)	78.5±11.0	78.6±10.3	78.3±11.6
Pulse (beats/min)	69.9±11.0	68.7±11.6	71.2±10.4
Arterial PWV (m/s)	19.29±3.95	19.31±4.05	19.28±3.86
Hb (g/100 ml)	13.6±1.3	14.1±1.4	13.1±1.0
BUN (mg/100 ml)	18.9±4.9	19.6±4.6	18.3±5.0
Creatinine (mg/100 ml)	0.85±0.23	0.96±0.22	0.75±0.18
Total protein (g/100 ml)	7.2±0.35	7.2±0.35	7.2±0.36
Total cholesterol (mg/100 ml)	218.2±43.0	205.6±32.1	230.4±48.6
Hb A1c (%)	5.22±0.66	5.23±0.75	5.20±0.57
CRP (mg/100 ml)	0.10±0.23	0.10±0.17	0.11±0.28
Hypertension (%)	8	9	7
Diabetes (%)	6	8	5
Hyperlipidemia (%)	20	10	29
Ischemic heart disease (%)	3	3	3
Cerebral infarction (%)	1	1	0
Alcohol consumption (%)	38	47	27
Smoking (%)	30	45	14

All values are mean±SD. BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; PWV, pulse wave velocity; BUN, blood urea nitrogen; CRP, C-reactive protein.

the 5′ flanking region; and rs1130864 (SNP4) and rs1205 (SNP5) in the 3′ untranslated region (Fig. 1).

Blood samples were collected from all subjects, and genomic DNA was extracted from the peripheral blood leukocytes by phenol and chloroform extraction (*25*). Genotyping for SNPs other than rs3091244 and rs1205 was performed using TaqMan® SNP Genotyping Assays obtained from Applied Biosystems (ABI, Foster City, USA), and genotyping for rs3091244 and rs1205 was performed using Custom TaqMan® SNP Genotyping Assays obtained from ABI. Because SNP2 was triallelic, the genotyping was performed using the C/A allele and C/T allele, and these results were combined.

Each 96-well plate contained 80 samples of an unknown genotype and 4 reaction mixtures containing reagents but no DNA (no-template control). The no-DNA control samples were necessary for the Sequence Detection System (SDS) 7700 signal processing, as outlined in the TaqMan Allelic Discrimination Guide (ABI). PCR plates were read on the SDS 7700 instrument using the end-point analysis mode of the SDS v1.6.3 software package (ABI). Genotypes were determined visually based on the dye-component fluorescent emission data depicted in the *X-Y* scatter-plot of the SDS software. Genotypes were also determined automatically by the signal processing algorithms in the software. The results of the two scoring methods were saved in separate output files for later comparison (*26*).

Biochemical Analysis

We used standard methods to measure hemoglobin levels, total plasma concentrations of protein and cholesterol, and serum concentrations of blood urea nitrogen and creatinine. Levels of hemoglobin A1c were measured using high-performance liquid chromatography. Plasma concentrations of CRP were measured using the latex-aggregation method. All biochemical analyses were performed at Bio Medical Laboratories Inc. (Tokyo, Japan).

PWV Measurement

PWV was non-invasively measured using a volume-plethysmographic apparatus (form PWV/ABI; Colin Co., Ltd., Komaki, Japan); the construction and measurement principles of this device have been described in detail elsewhere (*23*). The characteristic points of wave forms were determined automatically using the phase velocity theory. The time interval between the wave front of the brachial waveform and the wave front of the ankle waveform was designated as the time interval between the brachium and ankle (ΔT_{ba}). The distance between sampling points of baPWV was calculated automatically using the height of the subject. The path length from the heart to the brachium (L_b) was calculated using superficial measurements and the following equation: $L_b = 0.219 \times$ height of the subject (cm) $- 2.073$. The path length from the

Table 2. Genotype Distribution of Subjects with Normal and Elevated CRP Levels

SNP	Genotype		Normal CRP (276)[#]	Elevated CRP (14)[#]	*p* value	
					Fisher's exact test	Multiple logistic regression [OR/95% CI]
SNP1	Additive	CC	133	6		
		CT	109	5	0.59	
		TT	34	3		
	Dominant	CC+CT	242	11	0.40	
		TT	34	3		
	Recessive	TT+CT	143	8	0.79	
		CC	133	6		
SNP2	Genotype	CC	168	6		
		CA	70	2		
		CT	25	6	—	
		AA	7	0		
		AT	5	0		
		TT	1	0		
	With C allele	CC+CA+CT	263	14	—	
		AA+AT+TT	13	0		
	With A allele	CA+AA+AT	82	2	0.36	
		CC+CT+TT	194	12		
	With T allele	CT+AT+TT	31	6	0.004**	0.002** [7.1/2.1–24]
		CC+CA+AA	245	8		
SNP3	Additive	GG	266	14		
		GC	10	0	—	
		CC	0	0		
	Dominant	GG+GC	276	14	—	
		CC	0	0		
	Recessive	CC+GC	266	14	—	
		GG	10	0		
SNP4	Additive	CC	245	8		
		CT	30	6	—	
		TT	1	0		
	Dominant	CC+CT	275	14	0.75	
		TT	1	0		
	Recessive	TT+CT	245	8	0.004**	0.002** [7.1/2.1–24]
		CC	31	6		
SNP5	Additive	GG	126	6		
		GA	113	4	0.25	
		AA	37	4		
	Dominant	GG+GA	239	10	0.12	
		AA	37	4		
	Recessive	AA+GA	150	8	1.0	
		GG	126	6		

Levels of CRP <0.3 mg/100 ml were designated as normal CRP, and levels of CRP ≥0.3 mg/100 ml were designated as elevated CRP. The *p* value of each genotype was calculated using Fisher's exact test. The *p* value of logistic regression was calculated using multiple logistic regression analysis with adjustment for age, sex, body mass index, systolic blood pressure and the level of total cholesterol and hemoglobin A1c. CRP, C-reactive protein; OR, odds ratio; 95% CI, 95% confidence interval. [#]Number of subjects. ***p*<0.01.

heart to the ankle (L_a) was calculated using the following equation: $L_a = 0.8129 \times$ height of the patient (cm) + 12.328. We calculated baPWV using the following equation: baPWV $= (L_a - L_b)/\Delta T_{ba}$. The larger value of PWV obtained for each subject (left side *vs*. right side) was used for the analysis. Subjects with ankle brachial indexes of <0.8 were excluded from

Table 3. Genotype Distribution of Subjects with Normal and Elevated PWV

SNP	Genotype		Elevated PWV (280)#	Normal PWV (11)#	*p* value	
					Fisher's exact test	Multiple logistic regression [OR/95% CI]
SNP1	Additive	CC	134	3		
		CT	111	6	0.38	
		TT	35	2		
	Dominant	CC+CT	245	9	0.64	
		TT	35	2		
	Recessive	TT+CT	146	8	0.23	
		CC	134	3		
SNP2	Genotype	CC	170	4		
		CA	70	3		
		CT	27	4	—	
		AA	7	0		
		AT	5	0		
		TT	1	0		
	With C allele	CC+CA+CT	267	11	—	
		AA+AT+TT	13	0		
	With A allele	CA+AA+AT	82	3	1.0	
		CC+CT+TT	198	8		
	With T allele	CT+AT+TT	33	4	0.038*	0.18 [0.15/0.009–2.4]
		CC+CA+AA	247	7		
SNP3	Additive	GG	270	11		
		GC	10	0	—	
		CC	0	0		
	Dominant	GG+GC	280	11	—	
		CC	0	0		
	Recessive	CC+GC	270	11	—	
		GG	10	0		
SNP4	Additive	CC	247	7		
		CT	32	4	—	
		TT	1	0		
	Dominant	CC+CT	279	11	—	
		TT	1	0		
	Recessive	TT+CT	33	4	0.038*	0.18 [0.15/0.009–2.4]
		CC	247	7		
SNP5	Additive	GG	127	3		
		GA	114	6	0.49	
		AA	39	2		
	Dominant	GG+GA	241	9	0.66	
		AA	39	2		
	Recessive	AA+GA	153	8	0.36	
		GG	127	3		

PWV <14 m/s was designated as normal PWV, and PWV ≥14 m/s was designated as elevated PWV. The *p* value of each genotype was calculated using Fisher's exact test. The *p* value of logistic regression was calculated using multiple logistic regression analysis with adjustment for age, sex, body mass index, systolic blood pressure and the level of total cholesterol and hemoglobin A1c. PWV, arterial pulse wave velocity; OR, odds ratio; 95% CI, 95% confidence interval. *$p<0.05$.

the analysis.

Statistical Analysis

The subjects were classified into two CRP groups: a normal

Table 4. Linkage Disequilibrium (D' below Diagonal and r^2 above Diagonal) for the 5 SNPs

D'	r^2				
	SNP1	SNP2	SNP3	SNP4	SNP5
SNP1		0.581	0.009	0.144	0.912
SNP2	1.000		0.005	1.000	0.530
SNP3	1.000	0.971		0.001	0.009
SNP4	1.000	1.000	0.662		0.132
SNP5	1.000	1.000	1.000	1.000	

Values of $D' > 0.5$ and values of $r^2 > 0.6$ are underlined. SNP, single nucleotide polymorphism.

Table 5. Haplotype Frequency Estimates

Haplotype	CRP polymorphism			Frequency of the haplotype
	SNP1	SNP2	SNP3	
H1	C	C	G	0.657
H2	T	A	G	0.154
H3	T	C	G	0.106
H4	T	T	G	0.065
H5	C	C	C	0.018

Haplotype frequencies >0.01 were estimated using SNPAlyze. CRP, C-reactive protein.

CRP (<0.3 mg/100 ml) and an elevated CRP (≥0.3 mg/100 ml) group (*27*). The subjects were also classified into two arterial PWV groups: a normal PWV (<14 m/s) and an elevated PWV (≥14 m/s) group.

The subjects were also classified into three SNP genotype groups: an additive, a dominant, and a recessive genotype group. For SNP2, the subjects were classified into four genotype groups: each genotype and genotypes with/without C allele, with/without A allele and with/without T allele groups. Fisher's exact test was performed for each of the genotype groups. For genotype groups with significant differences revealed by Fisher's exact test, we performed multiple logistic regression analysis with adjustment for age, sex, body mass index, systolic blood pressure and the level of total cholesterol and hemoglobin A1c. The contingency table including 0 was not examined. Differences in PWV between groups were analyzed by one-way ANOVA or *t*-test after normal distribution and homogeneity of variance were confirmed.

Linkage disequilibrium (LD) was analyzed for the five SNPs. D' with p values >0.5 was considered a haplotype block. One SNP was excluded when r^2 was above 0.6. Based on the genotype data, the frequency of each haplotype and diplotype was estimated using the expectation/maximization (EM) algorithm (*28*, *29*). SNPAlyze software for Windows, version 5.0 was used (DYNACOM Co., Ltd., Yokohama, Japan) to perform the LD and the haplotype and diplotype analyses; this software is available at the website: http://www.dynacom.co.jp/products/package/snpalyze/index.html. Haplotypes with a frequency of <0.01 were excluded from analysis. Analyses of diplotype frequency were performed using two diplotype groups: one with and one without the haplotype. Fisher's exact test was performed for each of the diplotypes. For groups with significant differences in Fisher's exact test, we performed multiple logistic regression analysis using the confounders mentioned above. Statistical analyses were performed using SPSS 12 for Windows (SPSS Inc., Chicago, USA), and differences were considered statistically significant at $p<0.05$.

Results

Table 1 shows the clinical characteristics of the subjects. All subjects were genotyped based on the five SNPs. All SNPs were in good agreement with Hardy-Weinberg equilibrium (data not shown).

Table 2 shows the comparison of levels of CRP among the additive, dominant and recessive genotypes. In the Fisher's exact test, there were significant differences in the distribution of the T allele of SNP2 (CT+AT+TT *vs*. CC+CA+AA) and the T allele of SNP4 (TT+TC *vs*. CC) between the two CRP groups. In the multiple logistic regression analyses, there were significant differences in the distribution of both genotypes of SNP2 ($p=0.002$; 95% confidence interval [CI], 2.1–24) and SNP4 ($p=0.002$; 95% CI, 2.1–24) between the two CRP groups.

Table 3 shows the comparison of arterial PWV among the additive, dominant and recessive genotypes. In the Fisher's exact test, there was a significant difference in distribution of the T allele of SNP2 and the T allele of SNP4 between the two PWV groups. However, in the multiple logistic regression analyses, there was no significant difference in distribution of the genotypes of SNP2 or SNP4 between the two PWV

Table 6. Diplotype Distribution of Subjects with Normal and Elevated CRP Levels

Haplotype	Diplotype	Normal CRP (276)[#]	Elevated CRP (14)[#]	*p* value	
				Fisher's exact test	Multiple logistic regression [OR/95% CI]
H1	With H1	239	11	0.42	
	Without H1	37	3		
H2	With H2	82	2	0.36	
	Without H2	194	12		
H3	With H3	51	3	0.73	
	Without H3	225	11		
H4	With H4	31	6	0.004**	0.002** [7.1/2.1–24]
	Without H4	245	8		
H5	With H5	10	0	—	
	Without H5	266	14		

Levels of CRP <0.3 mg/100 ml were designated as normal CRP, and levels of CRP ≥0.3 mg/100 ml were designated as elevated CRP. The *p* value of each genotype was calculated using Fisher's exact test. The *p* value of logistic regression was calculated using multiple logistic regression analysis with adjustment for age, sex, body mass index, systolic blood pressure and the level of total cholesterol and hemoglobin A1c. CRP, C-reactive protein; OR, odds ratio; 95% CI, 95% confidence interval. [#]Number of subjects. ** $p<0.01$.

Table 7. Diplotype Distribution of Subjects with Normal and Elevated PWV

Haplotype	Diplotype	Elevated PWV (280)[#]	Normal PWV (11)[#]	*p* value	
				Fisher's exact test	Multiple logistic regression [OR/95% CI]
H1	With H1	242	9	0.652	
	Without H1	38	2		
H2	With H2	82	3	1.0	
	Without H2	198	8		
H3	With H3	53	3	0.45	
	Without H3	227	8		
H4	With H4	33	4	0.038*	0.18 [0.13/0.018–0.88]
	Without H4	247	7		
H5	With H5	10	0	—	
	Without H5	270	11		

PWV <14 m/s was designated as normal PWV, and PWV ≥14 m/s was designated as elevated PWV. The *p* value of each genotype was calculated using Fisher's exact test. The *p* value of logistic regression was calculated using multiple logistic regression analysis with adjustment for age, sex, body mass index, systolic blood pressure and the level of total cholesterol and hemoglobin A1c. PWV, arterial pulse wave velocity; OR, odds ratio; 95% CI, 95% confidence interval. [#]Number of subjects. * $p<0.05$.

groups.

In the Student's *t*-test, there was a significant difference in PWV between the two genotypes of SNP3 (GG, 19.17±3.86; GC, 21.77±5.06; $p=0.039$).

Table 4 shows the LD analysis for the five SNPs. The fact that all values of D' were >0.5 indicates that all SNPs (SNP1–5) were located in a haplotype block. Because the r^2 of SNP1-SNP5 and SNP2-SNP4 were extremely large, the haplotype was constructed using SNP1, SNP2 and SNP3. Five possible haplotypes were predicted (Table 5).

The relationship between CRP levels and arterial PWV was compared using two diplotypes (with H1–H5 *vs*. without H1–H5) of each haplotype (Tables 6 and 7). In the Fisher's exact test, CRP levels differed significantly among subjects with different diplotypes built using the H4 (T-T-G) haplotype ($p=0.004$). Also, in the multiple logistic regression analyses, CRP levels differed significantly among subjects with different diplotypes built using the H4 haplotype ($p=0.002$; 95% CI, 2.1–24).

The levels of arterial PWV differed significantly among subjects with different diplotypes built using the H4 haplotype ($p=0.038$). However, in the multiple logistic regression analyses, arterial PWV did not differ significantly among subjects with different diplotypes built with H4 (Table 7).

In the Student's *t*-test, there was a significant difference in PWV between the two H5 (C-C-C) haplotypes (with H5,

21.77±5.06; without H5, 19.17±3.86; $p=0.039$).

Discussion

Atherosclerosis is thought to involve inflammatory processes (*1*, *2*). CRP, a major inflammatory marker, has been detected in atherosclerotic plaques (*3*), and has been suggested to be involved in the development of atherosclerosis (*4*). Elevated plasma CRP levels may be an atherothrombotic biomarker that provides additive prognostic information not only for coronary heart disease (*5*, *6*) but also for peripheral arterial disease (*8*). Also, elevated plasma CRP levels may be a marker that predicts the risk of future cardio- and/or cerebrovascular events in the elderly (*7*). Some SNPs in the human CRP gene have been reported to be associated with elevated basal CRP levels, while others have been associated with reduced basal CRP levels (*10–13*). Case control studies have shown that some SNPs in the human CRP gene are associated with coronary heart disease or type 2 diabetes mellitus. The relation between SNPs of the interleukin-6 gene and atherosclerosis has already been reported (*30*).

In the present study, we genotyped five SNPs in the CRP gene of elderly Japanese subjects, and assessed whether the SNPs were associated with serum CRP levels and arterial PWV. We observed significant correlations between serum CRP levels and the T alleles of SNP2 or SNP4. Although SNP4 has been associated with elevated basal CRP levels in Caucasians (*11*), there have been no reports of a similar correlation between SNP2 and serum CRP levels. However, SNP2 was triallelic, and we concluded that SNP2 was more valuable than biallelic SNPs as a genetic marker. The C allele of SNP3 significantly correlated with arterial PWV. Thus, SNP3 appears to be a predictor of atherosclerosis in the elderly. It was difficult to assess whether SNP4 is an antiatherosclerotic marker. More controlled trials with a greater number of cases are needed to clarify the relationship between SNP4 and arterial PWV. The relationship between elevated CRP levels and progression of atherosclerosis is well documented, and the present results appear to conflict with the currently available evidence (*21*). However, arteriosclerosis is a multifactorial disorder, and CRP is just one of its risk predictors. Also, the five SNPs examined in the present study are nonfunctional, but their association with CRP levels and arterial PWV suggests that they are useful genetic markers.

It is possible to estimate haplotype frequencies using the EM algorithm with unrelated individuals under Hardy-Weinberg equilibrium. In addition, the EM algorithm allows estimation of the diplotype present in each individual. It is thought that correlation analysis using haplotypes reduces the risk of false positives, compared with correlation analysis using only SNPs, because haplotype correlation is influenced by allele frequency and linkage disequilibrium. Therefore, we conclude that correlation analysis using haplotypes is a relatively powerful technique for association studies.

In the present study, haplotypes were constructed using three SNPs (SNP1, SNP2 and SNP3), based on the results of LD analysis. The diplotype analysis showed that CRP levels were significantly greater in subjects with the H4 (T-T-G) haplotype than in other subjects. The diplotype analysis also showed that PWV was significantly greater in subjects with the H5 (C-C-C) haplotype than in other subjects. These results suggest that the H4 and H5 haplotypes are useful genetic markers for CRP levels and atherosclerosis, respectively.

In conclusion, the present results indicate that SNP2 and SNP4 are associated with elevated baseline plasma CRP levels in Japanese. Also, the H4 haplotype of the CRP gene is a genetic marker for elevated plasma CRP levels. In addition, SNP3 and the H5 haplotype of the CRP gene appear to be susceptibility markers for atherosclerosis.

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