C-Reactive Protein Gene Polymorphisms and the Risk of Atrial Fibrillation in a Chinese Population in Taiwan

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Background: Elevated plasma C-reactive protein (CRP) levels can be used to predict an increased risk of future atrial fibrillation (AF). However, several single polynucleotide polymorphisms (SNPs) in the *CRP* gene affect CRP levels. This study aims to elucidate the correlation between CRP gene polymorphisms and the risk of AF among a Chinese population in Taiwan.

Methods: A total of 200 patients with AF and 240 age- and gender-comparable control subjects were enrolled in this study. From these patients, five SNPs in the CRP gene were selected and genotyped.

Results: Patients with AF had significantly higher plasma CRP levels than the controls. In the total study population, the minor alleles of rs3091244 and rs1205 were significantly associated with higher CRP level ($p = 0.001$ and 0.045, respectively). The frequency of rs1800947 minor allele (C) was significantly higher in patients with AF than that in control subjects (12.8% and 4.6%, respectively; $p < 0.001$). On multivariate analysis, the presence of the C allele of rs1800947 was significantly and independently associated with AF after adjustment for age, gender, body mass index, hypertension, diabetes, smoking, hypercholesterolemia, coronary artery disease, concomitant medication, and CRP levels (odds ratio = 3.21; 95% confidence interval = 1.54-6.68; $p = 0.01$). Haplotype analysis further verified that the rs3091244C and rs1800947C bi-loci haplotype was significantly overpresented in patients with AF than in the controls.

Conclusions: Our results suggest that the presence of the C allele of rs1800947 may indicate susceptibility to AF in a Chinese population in Taiwan.

Key Words: Atrial fibrillation • C-reactive protein • Polymorphism

INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia encountered in clinical practice, leads to increased morbidity and mortality and creates a substantial burden on the health care system.[1-5] There have been remarkable advances in the understanding of AF mechanisms over the past few decades.[6-10] Growing evidence suggests that inflammation plays a role in the pathogenesis of several cardiovascular diseases, including AF. The link between inflammation and the initiation of AF was suggested by the observation of AF following inflammatory processes such as cardiac surgery, myocarditis, and pericarditis. In some studies, AF was suspected to cause "atrial myocarditis" and subsequent atrial remodeling, resulting in its own maintenance and recurrence.[11-14] Of note, pharmacological agents with anti-inflammatory

Received: February 22, 2013 Accepted: April 26, 2013
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properties, such as statins, corticosteroids, and angiotensin-converting enzyme inhibitors (ACEIs), have demonstrated the ability to attenuate atrial remodeling and AF burdens in animal studies and clinical trials.[13]

Chronic low-grade inflammation, characterized by elevated C-reactive protein (CRP) levels, is associated with increased cardiovascular events.[14] CRP, an acute-phase protein, is synthesized by hepatocytes in response to interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) under inflammatory circumstances. Elevated plasma CRP levels predict an increased risk of AF development and recurrence after either electrocardioversion or pulmonary vein isolation.[11,15-17] However, the causal contribution of CRP to AF is yet to be determined. Population-based studies have proposed that there may be a genetic predisposition for the development of AF.[18,19] Family studies have revealed substantial heritability (27-40%) of CRP levels.[20-22] Several single nucleotide polymorphisms (SNPs) in the *CRP* gene have been documented to be associated with circulating CRP concentrations. Whether there is a causal association between these genetic polymorphisms and the development of AF remains controversial.[17,23] The aim of this study was to elucidate the correlation between CRP gene polymorphisms and the risk of AF among a Chinese population in Taiwan.

MATERIALS AND METHODS

Study population

Our study enrolled patients who were < 65 years of age and had unexplained causes of AF. Patients who had a history of hyperthyroidism, significant valvular heart disease (> grade II mitral regurgitation and/or aortic regurgitation), or congestive heart failure (left ventricular ejection fraction < 50%) were excluded. The control group with sinus rhythm (SR) that was of comparable age and gender, was recruited from a population receiving routine health examinations and a population receiving regular hypertension treatment in an outpatient clinic. The protocols were approved by the local Research Ethics committees, and written informed consent was obtained from each subject.

Clinical assessment

The presence of AF in our subjects was documented by patient history, serial electrocardiograms (ECGs), and/or ambulatory ECG monitoring. Transthoracic echocardiography was performed to assess left atrial and left ventricular functions and to detect significant valvular diseases. Left atrial enlargement and left ventricular dysfunction were defined as diameter > 40 mm and ejection fraction < 50%, respectively. Hypertension was defined as blood pressure $\geq$ 140/90 mmHg and/or the use of antihypertensive medication. Definitions of hypercholesterolemia and diabetes mellitus were made in accordance with the third report of the National Cholesterol Education Program and the guidelines of the American Diabetes Association, respectively.

Genomic DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the Puregene DNA Isolation Kit (Qiagen, Minneapolis, MN, USA). Five SNPs were chosen for use in the genetic association study, according to an earlier study by Teng et al.[24] Oligonucleotide primers were generated to amplify fragments of genomic DNA containing SNPs reported on the GenePipe database (http://genepipe.ngc.sinica.edu.tw/visualsnp) and the NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP). The SNPs were placed in order of their position in the CRP gene. SNPs rs2794521 and rs3091244 were in the promoter region, SNP rs1800947 was in the exon 2 region, SNPs rs1130864 and rs1205 were in the 3′ untranslated region. Genotyping of the rs2794521, rs3091244, rs1800947, and rs1130864 SNPs was performed by polymerase chain reaction with restriction enzyme digestion (PCR-RFLP) as described previously.[24] Genotyping of the rs1205 SNP was performed using TaqMan SNP Genotyping Assays obtained from Applied Biosystems (ABI, Foster City, CA, USA). For quality control purposes, approximately 10% of the samples were re-genotyped in a blinded fashion and the same results were obtained. To confirm the genotyping performed by PCR-RFLP, a random sampling of the subjects was re-genotyped by direct sequence analysis using a commercial sequencing service and the primers previously used for PCR amplification.

Statistical analysis

The clinical characteristics of the continuous variables are expressed as means $\pm$ standard deviation and

tested using the 2-sample *t*-test or analysis of variance (ANOVA). The chi-square test was used to examine the differences in categorical variables and to compare the allele and genotype frequencies. The false discovery rate method was used to correct for multiple comparisons where applicable. CRP was logarithmically transformed prior to statistical analysis to adhere to a normality assumption. Binary logistic regression analysis was used to evaluate the independent effect of genotype on the risk of AF after adjustment for age, gender, body mass index (BMI), CRP, hypertension, diabetes, smoking, hypercholesterolemia, coronary artery disease (CAD), and concomitant medication. The analysis of deviation from Hardy-Weinberg equilibrium, estimation of linkage disequilibrium (LD) between polymorphisms, and association of haplotypes with AF were performed using SNPStats software (available at http://bioinfo.iconcologia.net/SNPstats).[25] A permutation test for significant differences in the haplotype frequencies in the case and control groups was performed using PHASE software (version 2.1).[26]

RESULTS

A summary of the demographic and clinical characteristics of the study population is shown in Table 1. Among the 440 subjects, 200 had AF and 240 were controls. No statistical differences were observed between the 2 groups in terms of age, gender, BMI, hypertension, diabetes mellitus, smoking, hypercholesterolemia, and history of CAD. Plasma CRP levels and concomitant medication used at baseline, including angiotensin receptor blockers, β-blockers, calcium antagonists, diuretics, statins, digoxin, aspirin, and oral anticoagulants were significantly higher in patients with AF than in the control subjects.

Table 2 presents the distribution of genotype and allele frequency for CRP polymorphisms in the study population according to the subject's AF status. No significant deviation from the Hardy-Weinberg equilibrium was detected for the 5 study SNP polymorphisms either for the cases (p = 1.00, 0.68, 0.75, 1.00, and 1.00 for SNPs rs2794521, rs3091244, rs1800947, rs1130864, and

Table 1. Demographic and clinical characteristics of the study population

	Controls (n = 240)	AF patients (n = 200)	p
Age, years	55.7 ± 7.6	56.9 ± 8.4	0.14
Gender (M/F)	172/68	145/55	0.85
BMI, kg/m^2	25.3 ± 3.2	25.5 ± 4.5	0.68
Hypertension, n (%)	126 (52.5)	119 (59.5)	0.14
Diabetes mellitus, n (%)	17 (7.1)	21 (10.5)	0.20
Smoking, n (%)	62 (25.8)	45 (22.6)	0.43
Hypercholesterolemia, n (%)	25 (10.4)	21 (10.5)	0.98
CAD, n (%)	5 (2.1)	10 (5.0)	0.09
CRP level, mg/L*	2.4 ± 9.1 (235)	4.9 ± 15.4 (169)	< 0.001
paroxysmal/persistent, n (%)	-	109/91 (54.5/45.5)	
LA dimension > 40mm, n (%)	-	86 (43.0)	
ARB, n (%)	65 (27.1)	83 (41.5)	< 0.001
ACE inhibitor, n (%)	15 (6.2)	11 (5.5)	0.74
β-blocker, n (%)	56 (23.3)	88 (44.0)	< 0.001
Calcium antagonist, n (%)	71 (29.6)	79 (39.5)	0.03
Diuretic, n (%)	11 (4.6)	32 (16.0)	< 0.001
Digoxin, n (%)	0 (0.0)	34 (17.0)	< 0.001
Statin, n (%)	41 (17.1)	59 (29.5)	0.002
Aspirin, n (%)	17 (7.1)	85 (42.5)	< 0.001
Oral anticoagulant, n (%)	0 (0.0)	38 (19.0)	< 0.001

ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; LA, left atrium.

* The CRP level data of 5 controls and 31 patients were missing. CRP levels were logarithmically transformed prior to statistical analysis to adhere to a normality assumption; however, the untransformed data are shown.

rs1205, respectively) or for the controls (p = 1.00, 0.37, 1.00, 0.054, and 0.44 for SNPs rs2794521, rs3091244, rs1800947, rs1130864, and rs1205, respectively). All of these SNPs were in strong pairwise linkage disequilibrium (Supplement Table 1).

As shown in Table 2, the genotype distribution of the CRP rs1800947 was significantly different between the AF patients and the controls (p < 0.001). The frequency of rs1800947 GG homozygotes also differed significantly between the patients with AF and the controls (75.5% vs. 90.8%, p < 0.001). Additionally, the frequency of the rs1800947 minor allele (C) was significantly higher in patients with AF than that in the controls (12.8% and 4.6%, respectively; p < 0.001). The difference remained statistically significant after multiple comparisons adjustment with a false discovery rate. Although the allelic distribution of the CRP rs3091244 tri-allele variant was significantly different between patients with AF and the controls (p = 0.041), the difference became insignificant after multiple testing adjustments. No significant difference was observed in genotype or allele distribution for the other 3 CRP polymorphisms between the patients with AF and the controls (Table 2).

Plasma CRP levels according to genotype status are compared in Table 3. CRP level data were missing for 5 controls and 31 patients with AF. Subjects with CRP levels > 10 mg/L (5 controls and 14 patients with AF) were considered to have an infection and were excluded from the analysis. In the total study population, using the dominant model, the minor alleles of rs3091244 and rs1205 were significantly associated with higher CRP level (p = 0.001 and 0.045, respectively) after adjustment for age, gender, BMI, hypertension, diabetes, smoking, hypercholesterolemia, CAD, and concomitant medication. In contrast, there were no significant differences between the rs2794521, rs1800947, and rs1130864 genotypes and CRP levels in the total study population. In the control group, the association between the minor alleles of rs3091244 and higher CRP levels remained significant (p = 0.001), but the association between rs1205 and CRP level was insignificant due to the small sample size (p = 0.089). Notably, none of the 5 SNPs were associated with CRP levels in patients with AF. It is possible that the high levels of many inflammatory risk factors seen in patients with AF may mask the genetically associated changes.

Table 2. Distribution of genotype and allele for C-reactive protein polymorphisms in 200 patients with atrial fibrillation (AF) and 240 controls

	Controls (n = 240)	AF patients (n = 200)	p	p*
rs2794521				
GG	7 (2.9%)	4 (2%)	0.519	0.519
GA	70 (29.2%)	50 (25.3%)		
AA	163 (67.9%)	144 (72.7%)		
G/A	17.5/82.5	14.6/85.4	0.254	0.254
rs3091244				
TT	2 (0.8%)	1 (0.5%)	0.232	0.290
AA	10 (4.2%)	4 (2.0%)		
AT	4 (1.7%)	3 (1.5%)		
CT	14 (5.8%)	25 (12.5%)		
AC	68 (28.3%)	46 (23%)		
CC	142 (59.2%)	121 (60.5%)		
T/A/C	4.6/19.2/76.2	7.5/14.2/78.2	0.041	0.103
rs1800947				
CC	0	2 (1%)	< 0.001	0.001
CG	22 (9.2%)	47 (23.5%)		
GG	218 (90.8%)	151 (75.5%)		
C/G	4.6/95.4	12.8/87.2	< 0.001	< 0.001
rs1130864				
TT	2 (0.8%)	1 (0.5%)	0.150	0.28
TC	16 (6.7%)	25 (12.6%)		
CC	222 (92.5%)	173 (86.9%)		
T/C	4.2/95.8	6.8/93.2	0.086	0.108
rs1205				
GG	46 (19.2)	31 (15.6)	0.168	0.28
AG	125 (52.3)	95 (47.7)		
AA	68 (28.5)	73 (36.7)		
G/A	45.4/54.6	39.4/60.6	0.076	0.108

AF, atrial fibrillation.
* Multiple testing correction using the false discovery rate.

We used multiple logistic regression analysis to evaluate the association between CRP genotypes and AF risk (Table 4). The probability of AF was significantly higher in subjects with the C allele of rs1800947 than in non-carriers [odds ratio (OR) = 3.21; 95% confidence interval (CI) = 1.54-6.68; p = 0.002] after adjustment for age, gender, BMI, hypertension, diabetes, smoking, hypercholesterolemia, CAD, log CRP level, and concomitant medication. The association remained statistically significant after adjustment for CRP levels and multiple testing (p = 0.01).

Given that only rs3091244 is a proven functional

Table 3. *CRP* genotypes in the dominant model and CRP levels for 200 patients with atrial fibrillation (AF) and 240 controls

	Total	p value	p* value	Controls (n = 240)	p value	p* value	AF patients (n = 200)	p value	p* value
rs2794521									
GG + GA	1.55 ± 1.75 (118)	0.117	0.147	1.41 ± 1.83 (73)	0.113	0.280	1.78 ± 1.59 (45)	0.783	0.489
AA	1.69 ± 1.71 (266)			1.63 ± 1.67 (157)			1.79 ± 1.78 (109)		
rs3091244									
CT + TT	1.96 ± 1.71 (32)	0.001	0.003	2.14 ± 1.70 (15)	< 0.001	0.002	1.80 ± 1.75 (17)	0.389	0.534
CA + AA + AT	2.08 ± 2.07 (114)			2.11 ± 2.18 (77)			2.00 ± 1.82 (37)		
CC	1.41 ± 1.49 (239)			1.19 ± 1.30 (138)			1.72 ± 1.68 (101)		
Non CC	2.05 ± 1.99 (146)	< 0.001	0.001	2.12 ± 2.10 (92)	< 0.001	0.001	1.94 ± 1.79 (54)	0.198	0.479
rs1800947									
CC + CG	1.73 ± 1.98 (60)	0.979	0.911	1.00 ± 1.15 (22)	0.091	0.298	2.15 ± 2.24 (38)	0.392	0.266
GG	1.64 ± 1.67 (325)			1.62 ± 1.77 (208)			1.68 ± 1.50 (117)		
rs1130864									
TT + TC	1.61 ± 1.32 (36)	0.389	0.710	1.83 ± 1.60 (18)	0.184	0.189	1.39 ± 0.97 (18)	0.527	0.224
CC	1.66 ± 1.76 (348)			1.54 ± 1.74 (212)			1.85 ± 1.79 (136)		
rs1205									
GG + GA	1.73 ± 1.73 (256)	0.110	0.045	1.65 ± 1.77 (162)	0.071	0.089	1.86 ± 1.68 (94)	0.390	0.590
AA	1.47 ± 1.66 (127)			1.26 ± 1.51 (67)			1.70 ± 1.79 (60)		

CRP level data were missing for 5 controls and 31 patients with AF. Subjects with CRP > 10 mg/L (5 controls and 14 patients with AF) were excluded from the analysis.

* Adjustment for age, gender, body mass index, hypertension, diabetes, smoking, hypercholesterolemia, coronary artery disease, and concomitant medication.

CRP was logarithmically transformed prior to the statistical analysis to adhere to a normality assumption; however, the untransformed data are shown.

Table 4. Multiple logistic regression analysis of the association between *CRP* genotypes and arterial fibrillation (AF) risk

	Controls (n = 240)	AF patients (n = 200)	Odds ratio (95% CI)*	p*	p†
rs2794521					
GG + GA	77 (32.1%)	54 (27.3%)	1.03 (0.57-1.84)	0.935	0.935
AA	163 (67.9%)	144 (72.7%)			
rs3091244					
CT + TT	16 (6.7%)	26 (13.0%)	1.58 (0.62-4.02)	0.098	
CA + AA + AT	82 (34.2%)	53 (26.5%)	0.59 (0.32-1.10)	0.339	
CC	142 (59.2%)	121 (60.5%)			
Non CC	98 (40.8%)	79 (39.5%)	0.74 (0.42-1.30)	0.292	0.385
rs1800947					
CC + CG	22 (9.2%)	49 (24.5%)	3.21 (1.54-6.68)	0.002	0.010
GG	218 (90.8%)	151 (75.5%)			
rs1130864					
TT + TC	18 (7.5%)	26 (13.1%)	1.57 (0.66-3.75)	0.308	0.385
CC	222 (92.5%)	173 (86.9%)			
rs1205					
GG + GA	171 (71.5%)	126 (63.3%)	0.70 (0.39-1.24)	0.221	0.385
AA	68 (28.5%)	73 (36.7%)			

* Adjustment for age, gender, body mass index, hypertension, diabetes, smoking, hypercholesterolemia, coronary artery disease, log C-reactive protein (CRP) level, and concomitant medication; † Multiple testing correction by false discovery rate.

variant and that only rs1800947 showed a significant association with AF in this study, we conducted a haplotype analyses based only on these 2 SNPs. Haplotype frequencies were separately estimated for 200 patients and 240 controls using an expectation-maximization algorithm. As shown in Table 5, the frequency of haplotype rs3091244C/rs1800947C was significantly higher in patients with AF than in the controls. The overall haplotype frequency profiles also differed significantly between patients with AF and control subjects (p = 0.01 based on 1,000 permutations).

Table 5. Frequencies of the common haplotypes derived from *CRP* rs3091244 and rs1800947 in the study population

	rs3091244	rs1800947	Total	Controls	AF
H1	C	G	0.688814	0.716733	0.65531
H2	A	G	0.169149	0.191604	0.142203
H3	C	C	0.082777	0.045767	0.12719
H4	T	G	0.059083	0.045829	0.074987
H5	A	C	0.000169	0.000063	0.000297

p value for testing H0: cases – controls = 0.01 (based on 1,000 permutations).

DISCUSSION

This study analyzed the association between CRP gene polymorphisms and the susceptibility to AF in an ethnically Chinese population in Taiwan. Our findings did not reproduce those of an earlier report of the association between the minor allele of CRP rs3091244 and the major allele of rs1800947 and AF in Chinese individuals.[23] In contrast, our results suggest that the presence of the minor allele of rs1800947 may confer susceptibility to AF among ethnically Chinese Taiwanese individuals.

Consistent with the findings of earlier studies, we found that the CRP level, an indicator of chronic inflammation state, was significantly higher in individuals with AF than in the controls. In our study, however, the lack of an effect of *CRP* gene polymorphisms upon AF through modulating CRP levels indicates that elevated CRP level may be an epiphenomenon associated with AF development. Cytokines including TNF-α, IL-1 and other factors act synergistically with IL-6, the major inducer of the *CRP* gene, to enhance its effect on CRP production. These proinflammatory cytokines have been linked to the pathogenesis of AF.[27-29] As a downstream marker of the inflammatory cascade, CRP is non-specific and parallels the elevation of other inflammatory markers such as the erythrocyte sedimentation rate. Instead of being part of the causal pathway of AF, the elevated CRP level could be an "innocent bystander". In addition, polymorphisms in IL-1,[30,31] IL-6,[32,33] and TNF-α[34] as well as the *HNF1*[35] and *ATF3*[36] genes have been demonstrated to affect baseline plasma CRP levels. The influence on baseline CRP levels due to only CRP polymorphisms may not be large enough to alter the risk of AF.

The 5 studied SNPs of the *CRP* gene have been reported to be associated with cardiovascular diseases and differences in CRP levels.[37-42] Of note, the triallelic rs3091244 SNP is so far the only functional CRP polymorphism. Using luciferase reporter assays, Szalai et al. studied transcription activities at baseline and in response to IL-6 among different promoter haplotypes and found that haplotypes harboring the A or T alleles of SNP rs3091244 were associated with the highest promoter activity and baseline CRP levels.[43] Chang et al. also recently confirmed that the rs3091244 triallelic SNP captured the information of the CRP gene promoter activity and that subjects with haplotypes carrying the A or T allelic variants had higher CRP gene promoter activity; thus, a higher CRP level was seen in a Taiwanese population.[23] Moreover, they reported that the allele frequency of rs3091244 *A* was significantly higher in patients with AF than in the control subjects. The minor (C) allele frequency of exon 2 rs1800947 polymorphism, which was near complete LD with the major (C) allele of rs3091244 with a lower promoter activity, was also significantly lower in patients with AF compared with the controls. In their case-control study, the protective effect of minor allele (C) of SNP rs1800947 on AF remained significant in multivariable analysis. However, the association became insignificant after adjustment of CRP levels, suggesting that plasma CRP is the cause of the association between rs1800947 and the risk of AF. In our study, the significant associations of A/T alleles of rs3091244 with CRP levels were substantially consistent in the controls and the total study population, while they became insignificant in patients with AF.

In contrast to Chang's results, our study showed that the presence of the C allele of rs1800947 was sig-

nificantly and independently associated with an increased risk of AF. Interestingly, patients with AF who carry the C allele of rs1800947 had paradoxically higher, although insignificantly, mean plasma CRP levels compared to patients with AF who carry the rs1800947 GG genotype. In our study, the C allele of rs1800947 is also consistently LD with major allele of rs3091244, and was expected to be associated with lower plasma CRP levels as shown in our controls. Thus, our findings suggest that elevated plasma CRP levels in patients with AF are substantially affected by non-genetic factors.

There are several possible reasons for the apparent paradoxical findings between our results and those of Chang et al., including the heterogeneity and broad spectrum of patients enrolled, artifacts of a small sample size, and gene-gene and gene-environmental interactions. In a TCVGHAGE study,[44] Sheu et al. investigated the effect of CRP polymorphisms on plasma CRP concentrations in 369 healthy Chinese veterans living in Taiwan. The allele frequencies were: rs2794521 A/G, 0.825/0.175; rs3091244 C/A/T, 0.77/0.17/0.06; rs1800947 G/C, 94.1/5.9; and rs1205 A/G, 57.5/42.5. These findings are similar to those found in our controls as well as in our earlier report.[24] Interestingly, the distribution of the allele frequencies for rs3091244 and rs1800947 in the controls of the Chang et al. study were more compatible with those in the patients with AF in our study. The discrepancies in allele frequencies and genotype distribution between the Chang study and our study likely indicate differences in subject characteristics and the burden of cardiovascular disease risk factors. Their controls comprised patients who were recruited from cardiovascular clinics and adult cardiology wards, and they had a higher mean age, BMI, and prevalence of CAD, diabetes mellitus, hypertension, dyslipidemia, smoking, and statin use than controls and patients with AF in our study. Moreover, the patients with AF in Chang's study did not exclude patients with significant valvular heart disease or patients with heart failure, and they were considerably older than our patients. Another possibility is that the observed association between rs1800947 (a synonymous polymorphism) and AF in this study could be through the LD with an unknown variant other than rs3091244 in or adjacent to the *CRP* gene. On the other hand, our study's sample size might be too small to show a small but significant risk of AF associated with triallelic SNP rs3091244. Finally, both the observed differences between CRP polymorphisms and AF in the Chang study and our study may be due to chance rather than a real difference. A recent large genetic study in a Danish population utilizing the Mendelian randomization approach showed that elevated plasma CRP levels are strongly associated with an increased risk of AF; however, CRP gene polymorphisms and genetically elevated CRP levels are not similarly associated.[17]

Our study had several limitations. The main limitation was its small sample size, which was not analyzed in any functional manner and showed only an arguable relationship with disease. Second, the CRP level information in the AF group was incomplete. Finally, our study has a cross-sectional design and provides no information about the effect of the CRP polymorphisms on the progression of AF or its clinical outcome.

CONCLUSIONS

In conclusion, our results suggested that the rs1800947 in the CRP gene was, independent of CRP levels and traditional risk factors of AF, significantly associated with susceptibility to AF in a Chinese population living in Taiwan. A larger prospective and longitudinal study would be necessary to fully assess the significance of this polymorphism on the risk of AF.

ACKNOWLEDGEMENT

This study was supported by a grant from Chang Gung Memorial Hospital (CMRPG 3A1161) to L-A Hsu and a grant from Chang Gung Memorial Hospital (CMRPG 3B0991) to C-T Kuo.

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Supplement Table 1. Linkage disequilibrium analysis of CRP polymorphisms

D′

	rs2794521	rs3091244	rs1800947	rs1130864	rs1205
rs2794521	-	0.998 (< 0.0001)	0.9957 (0.0001)	0.9543 (0.0032)	0.9992 (< 0.0001)
rs3091244	-	-	0.997 (< 0.0001)	0.9658 (< 0.0001)	0.9783 (< 0.0001)
rs1800947	-	-	-	0.986 (0.0366)	0.9984 (< 0.0001)
rs1130864	-	-	-	-	0.9473 (< 0.0001)
rs1205	-	-	-	-	-

The value represents D′ (p value)

r

	rs2794521	rs3091244	rs1800947	rs1130864	rs1205
rs2794521	-	-0.2388	-0.1317	-0.0998	0.5092
rs3091244	-	-	-0.1631	0.4222	0.6167
rs1800947	-	-	-	-0.0705	-0.2592
rs1130864	-	-	-	-	0.261
rs1205	-	-	-	-	-