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Interleukin-6 Promoter Polymorphisms and Susceptibility to Atrial Fibrillation in Elderly Han Chinese Patients with Essential Hypertension

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There is an accumulating body of evidence indicating a strong association between inflammation and the pathogenesis of atrial fibrillation (AF). Interleukin-6 (IL-6) is a pleiotropic cytokine, functions as a mediator of inflammatory response, and has both proinflammatory and anti-inflammatory properties. The aim of the present study was to investigate the association of the −634C/G polymorphism of the *IL-6* gene with AF in elderly Han Chinese patients with essential hypertension (EH). A total of 169 elderly patients with EH were eligible for this study. Patients with AF ($n=75$) were allocated to the AF group, and 94 subjects without AF to the control group. The polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique was used to assess the genotype frequencies. The distribution of the *IL-6* −634C/G genotypes (CC, CG, and GG) was 67.02%, 30.85%, and 2.13% in the controls, and 50.67%, 40.00%, and 9.33% in AF subjects, respectively ($P=0.0312$). The frequency of the G allele in the AF group was significantly higher than that in the control group (29.33% vs. 17.55%, $P=0.0103$). Compared with the CC and CG genotypes, the GG homozygote had a 4.7353-fold increased risk of AF [95% confidence interval (CI) = 0.9537–23.5116, $P=0.0382$]. These findings suggest that the *IL-6* −634C/G polymorphism is associated with AF, and the G allele has increased risk of AF in elderly Han Chinese patients with EH.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in clinical practice, affecting 1%–2% of the general population (Go and others 2001; Pan and others 2006; Camm and others 2010). The prevalence of AF is strongly age dependent, affecting ~0.5% of individuals aged at 40–50 years and 5%–15% of individuals at 80 years. AF not only is an independent risk factor for death but also confers a significant risk of morbidity from stroke associated with cardiogenic thromboembolism (Nakamura and others 2003; Gao and others 2011a).

Essential hypertension (EH) is the most common cardiac condition associated with AF (Verdecchia and others 2003). The risk of AF in hypertensive compared with normotensive subjects was increased by 1.9 times in the Framingham Heart Study (Kannel and others 1982) and 1.4 times in the Manitoba Follow-up Study (Krahn and others 1995). However, the mechanisms relating hypertension to AF are poorly understood.

Recently, several lines of evidence support a strong association between inflammation and the pathogenesis of AF. Histological evidence to support the association between inflammation and AF has been derived from several sources (Frustaci and others 1997; Kamiyama 1998; Verheule and others 2003). In addition, some studies have shown that concentrations of inflammatory mediators or markers, such as interleukin (IL)-6 and high-sensitivity C-reactive protein, were increased in patients with AF and were associated with unsuccessful cardioversion (Dernellis and Panaretou 2001; Lip and others 2007). Furthermore, treatment with anti-inflammatory agents, such as statins, in AF patients was associated with a significant decrease in the risk of arrhythmia recurrence after successful cardioversion (Siu and others 2003).

IL-6 is a pleiotropic cytokine of 23.7 kDa secreted by many cells of the immune system, cardiovascular components, and

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adipose tissue; functions as a mediator of inflammatory response; and has both proinflammatory and anti-inflammatory properties (Ravishankaran and others 2011; Kruttgen and Rose-John 2012). Circulating levels of IL-6 differ greatly between individuals (Smith and others 2008; Bennermo and others 2011). This difference is due to both genetic and environmental influences (Pantsulaia and others 2002). The human *IL-6* gene is located at chromosome 7p21 and contains 5 exons, and 3 single-nucleotide polymorphisms (SNPs) in the *IL-6* promoter region [−597G/A (rs1800797); −634C/G (rs1800796), and −174G/C (rs1800795)] have been reported to influence *IL-6* transcription, and −174G/C was in tight linkage disequilibrium with −597G/A (Cardellini and others 2005; Cherel and others 2009; Schulte and others 2011). However, the −174C allele is extremely rare, and the −634C allele is common in eastern Asian populations (Terry and others 2000; Saijo and others 2007; Koh and others 2009; Gao and others 2011b; Pan and others 2011), whereas in Caucasians, the −174C allele is relatively frequent, and the −634C allele is less frequent (Humphries and others 2001; Antonicelli and others 2005; Hamid and others 2005).

Based on these findings, we carried out a case–control study of the *IL-6* gene −634C/G polymorphism to test the association with AF in elderly Han Chinese patients with EH.

Subjects and Methods

Study subject

A total of 169 elderly patients with EH were eligible for this study. Patients with AF ($n=75$) were allocated to the AF group, and 94 subjects without AF to the control group. The study subjects were enrolled at the Affiliated Hospital of Nantong University. EH was defined according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) criteria (Chobanian and others 2003) as diastolic blood pressure equal to or over 90 mm Hg and/or systolic blood pressure equal to or over 140 mm Hg (average of 2 measurements) or on treatment with antihypertension therapy. AF was defined according to the European Society of Cardiology (ESC) Guidelines for the management of AF (Camm and others 2010) as replacement of sinus P waves by rapid oscillations or fibrillatory waves that varied in size, shape, and timing, which were associated with an irregular ventricular response when atrioventricular conduction was intact. The presence of AF was determined from history, followed by serial electrocardiogram or ambulatory electrocardiographic monitoring. Details of medical history, family history, and clinical symptoms were obtained from all participants using a standardized questionnaire, together with information of drug intake and cigarette smoking. Blood pressure, height, weight, and waistline were measured by trained physicians or nurses according to standardized protocols. Patients with acute coronary syndrome, hypertrophic cardiomyopathy, significant valvular disease, left ventricular dysfunction (ejection fraction <50%), and neoplastic, renal, liver, or thyroid diseases were excluded. All study participants were unrelated Han nationality residents over than 55 years. The study has been approved by the Medical Ethics Committee of Nantong University, and written informed consent was obtained from all participants.

Biochemical analysis

Venous blood samples were obtained after at least a 10-h overnight fast and then centrifuged at 2500 rpm for 30 min at 4°C and immediately stored −80°C until analysis. Total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides were measured as described previously (Pan and others 2009).

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes by the salting-out method with minimal modifications. IL-6 −634C/G genotypes were determined by PCR-RFLP as described previously (Chen and others 2011).

Statistical analysis

All continuous variables are expressed as the mean and standard deviation. Student's *t*-test and analysis of variance followed by the Newman-Keuls test were used to compare continuous variables from 2 groups and multiple groups, respectively. Genotypes and allele frequencies were obtained by direct count. Differences in the distribution of alleles and genotypes between the groups and deviations from the Hardy–Weinberg equilibrium were assessed by χ^2 test. All significant tests were 2-tailed and were considered statistically significant at $P<0.05$. SPSS for Windows version 11.0 (SPSS, Inc., Chicago, IL) was used for all statistical analyses.

Results

The clinical characteristics of all participants enrolled in the study are depicted in Table 1. No significant differences

Table 1. Clinical Characteristics of Atrial Fibrillation and Control Subjects

Characteristics	*AF (n=75)*	*Controls (n=94)*	P
Age (years)	71.63±8.62	71.25±8.17	0.7708
Gender (% male)	62.67	64.89	0.7646
SBP (mm Hg)	145.33±24.86	143.21±23.75	0.5713
DBP (mm Hg)	81.76±10.37	83.31±11.44	0.3632
BMI (Kg/m^2)	23.54±3.37	23.86±3.78	0.5671
LVEF (%)	59.86±6.21	61.27±6.59	0.1536
Left atrial dimension (mm)	48.16±7.13	37.42±6.82	0.0000
TC (mmol/L)	4.86±0.59	4.72±0.51	0.1001
LDL-C (mmol/L)	2.50±0.41	2.54±0.46	0.5566
HDL-C (mmol/L)	1.41±0.25	1.47±0.29	0.1576
TG (mmol/L)	1.60±0.52	1.53±0.48	0.3654
Diabetes mellitus (%)	21.33	24.47	0.6308
Smoking (%)	17.33	11.70	0.2974
Diuretics (%)	38.67	28.72	0.1724
Calcium antagonist (%)	48.00	48.94	0.9037
β-blocker (%)	34.67	26.60	0.2561
ACE inhibitor (%)	50.67	54.26	0.6425
ARB (%)	29.33	32.98	0.6118

AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body–mass index; LVEF, left ventricular ejection fraction; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

were seen between the 2 groups with regard to age, gender, body–mass index (BMI), blood pressure, left ventricular ejection fraction, serum lipid levels, diabetes, smoking status, and the use of antihypertensive drugs. However, compared with the controls, AF patients had a larger left atrial dimension.

Table 2 summarizes the distributions of the IL-6 −634C/G genotypes and their effects on clinical parameters for 2 groups. The genotype distribution among the subjects was in the Hardy–Weinberg equilibrium in both the control group ($\chi^2 = 0.4080$, $P = 0.5230$) and the AF group ($\chi^2 = 0.0928$, $P = 0.7603$). The distribution of the IL-6 −634C/G genotypes (CC, CG, and GG) was 67.02%, 30.85%, and 2.13% in the controls, and 50.67%, 40.00%, and 9.33% in AF subjects, respectively ($P = 0.0312$). The frequency of the G allele in the AF group was significantly higher than that in the control group (29.33% vs. 17.55%, $P = 0.0103$). There were no statistical differences in the gender, age, BMI, blood pressure, and serum lipid parameters between the genotypes in AF or control groups. However, AF patients with the CG or GG genotype had greater left atrial dimensions than did patients with the CC genotype ($P < 0.05$).

The association of the IL-6 −634C/G genotypes and alleles with AF is shown in Table 3. The GG genotype [$\chi^2 = 4.2960$, odds ratio (OR) = 4.7353, 95% confidence interval (CI) = 0.9537–23.5116, $P = 0.0382$] and the G allele ($\chi^2 = 6.5817$, OR = 1.9497, 95% CI = 1.1655–3.2616, $P = 0.0103$) were significantly associated with AF.

Table 3. Comparison of Interleukin-6 −634C/G Genotypes and Alleles in Atrial Fibrillation Patients and Controls

	χ^2	*Odds ratio (95% CI)*	P
CC vs. CG + GG	4.6401	0.5054 (0.2707–0.9435)	0.0312
CG vs. CC + GG	1.5366	1.4943 (0.7908–2.8236)	0.2151
GG vs. CC + CG	4.2960	4.7353 (0.9537–23.5116)	0.0382
CC vs. GG	5.5117	0.1723 (0.0340–0.8728)	0.0189
C vs. G	6.5817	0.5129 (0.3066–0.8580)	0.0103
G vs. C		1.9497 (1.1655–3.2616)	

CI, confidence interval.

Discussion

The major finding of the present study was that, for the first time, there is a strong association between the *IL-6* −634C/G polymorphism and the risk of developing AF in hypertensive patients. Compared with the CC and CG genotypes, the GG homozygote had a 4.7353-fold increased risk of AF (95% CI = 0.9537–23.5116, $P = 0.0382$). The G-allele carriers also had greater left atrial dimensions compared with the CC homozygotes in AF group. These findings support the hypothesis that inflammation plays a role in the underlying mechanisms of AF.

In the past few years, much attention has been devoted to assess the role of IL-6 in AF (Burzotta and others 2001). Elevated plasma IL-6 levels have been related to chronic (persistent and permanent) and new-onset AF and increased left atrial diameter (Psychari and others 2005; Gedikli and others 2007). In patients undergoing coronary artery bypass graft surgery, the development of postoperative AF was correlated with increased IL-6 levels and promoter polymorphisms of the *IL-6* gene (Burzotta and others 2001). Furthermore, in a cross-sectional study of 971 patients with coronary artery disease, among 6 inflammatory biomarkers, AF was associated with high IL-6 levels, and linked to the −174G/C polymorphisms in the promoter region of the *IL-6* gene (Marcus and others 2008).

As AF is often associated with other cardiac and systemic disorders, it is not generally appreciated that AF may be inherited. However, accumulating studies have provided evidence of a genetic contribution to AF. A few studies have identified Mendelian variants in selected families, which increase susceptibility to AF (Chen and others 2003; Ellinor and others 2003; Olson and others 2005). In addition, the future risk for offspring AF in parental compared with no parental AF was increased by 1.85 times in the Framingham Heart Study (Fox and others 2004) and 1.77 times in unselected families in Iceland (Arnar and others 2006). This risk is considerably greater for younger patients. Furthermore, most patients with AF have one or more identifiable risk

Table 2. Distribution of Interleukin-6 −634C/G Genotypes and Effects on Clinical Parameters

	AF (n = *75*)				*Controls* (n = *94*)			
Characteristics	*CC*	*CG*	*GG*	P	*CC*	*CG*	*GG*	P
Genotypes frequencies (*n*, %)	38 (50.67)	30 (40.00)	7 (9.33)		63 (67.02)	29 (30.85)	2 (2.13)	0.0312
Age (years)	71.89 ± 9.14	71.31 ± 8.24	71.57 ± 8.56	0.9636	71.33 ± 8.19	71.18 ± 8.14	69.79 ± 4.22	0.9644
Gender (% male)	63.16	63.33	57.14	0.9508	63.49	68.97	50.00	0.7945
SBP (mm Hg)	145.76 ± 24.92	144.76 ± 24.17	145.44 ± 24.73	0.9862	144.67 ± 23.81	140.07 ± 23.22	142.75 ± 13.61	0.6853
DBP (mm Hg)	82.28 ± 10.52	81.15 ± 10.10	81.57 ± 10.18	0.9034	83.17 ± 11.40	83.61 ± 11.45	83.30 ± 4.51	0.9852
BMI (Kg/m^2)	23.28 ± 3.07	23.83 ± 3.61	23.72 ± 3.33	0.7862	23.90 ± 3.84	23.81 ± 3.72	23.35 ± 1.88	0.9761
LVEF (%)	59.38 ± 5.94	60.56 ± 6.49	59.45 ± 6.12	0.7256	61.58 ± 6.77	60.60 ± 6.47	61.22 ± 2.45	0.8062
Left atrial dimension (mm)	45.73 ± 6.56	49.82 ± 7.85[a]	54.26 ± 8.23[a]	0.0065	37.10 ± 6.58	38.11 ± 6.97	37.56 ± 2.21	0.7965
TC (mmol/L)	4.97 ± 0.61	4.71 ± 0.52	4.92 ± 0.58	0.1781	4.78 ± 0.52	4.60 ± 0.47	4.63 ± 0.14	0.2753
LDL-C (mmol/L)	2.41 ± 0.38	2.62 ± 0.49	2.46 ± 0.40	0.1378	2.52 ± 0.45	2.59 ± 0.48	2.48 ± 0.23	0.7791
HDL-C (mmol/L)	1.44 ± 0.26	1.35 ± 0.22	1.51 ± 0.25	0.1752	1.51 ± 0.31	1.38 ± 0.26	1.53 ± 0.11	0.1434
TG (mmol/L)	1.54 ± 0.48	1.69 ± 0.57	1.53 ± 0.53	0.4717	1.49 ± 0.42	1.61 ± 0.52	1.59 ± 0.15	0.4891

[a] $P < 0.05$ in comparison with the CC genotype.

factors, but many or even most individuals with these same risk factors do not develop AF, indicating that there are probably genetic factors that predispose some of them to the AF. Several investigations have been trying to unravel some of these genetic backgrounds with the use of association studies. In some case–control studies, genetic polymorphisms of cardiac sodium channel (SCN5A) (Chen and others 2007), tissue inhibitors of matrix metalloproteinases-2 (Gai and others 2010), renin–angiotensin system (Tsai and others 2004; Wang and others 2010), cholesteryl ester transfer protein (Asselbergs and others 2006) were identified as risk factors for AF. A genome-scan analysis performed in 3 populations of European descent and a Chinese population found a strong association between 2 sequence variants at chromosome 4q25 and AF (Gudbjartsson and others 2007). Most recently, 3 SNPs at chromosome 4q25 (rs2200733, rs17570669, and rs3853445) in a case–control study of 790 American patients with AF and 1177 controls were considered for contributing to the pathogenesis of AF (Lubitz and others 2010).

Circulating levels of IL-6 vary widely within populations (Smith and others 2008; Bennermo and others 2011), and genetic factors are thought to play a major role, along with environmental factors, particularly inflammation (Pantsulaia and others 2002). The IL-6-coding sequence contains only a few very rare polymorphisms (Biasucci and others 1996). This fact has led to the hypothesis that the observed differences in the IL-6 concentration among individuals are influenced by variation in the *IL-6* gene promoter region (Smith and others 2008). However, the −174C allele is extremely rare, and the −634C allele is common in eastern Asian populations, whereas in Caucasians, the −174C allele is relatively frequent, and the −634C allele is less frequent (Terry and others 2000; Humphries and others 2001; Antonicelli and others 2005; Saijo and others 2007; Koh and others 2009; Gao and others 2011b; Pan and others 2011). Our previous report (Pan and others 2011) along with the studies conducted in Japanese and Koreans (Kitamura and others 2002; Shibata and others 2002; Paik and others 2007; Saijo and others 2007; Shin and others 2007; Jang and others 2008) indicates that IL-6-634C/G is associated with circulating levels of IL-6 in eastern Asians. Furthermore, it has been reported by several independent genetic studies that the *IL-6* −634C/G polymorphism was associated with the susceptibility to inflammatory conditions in Han Chinese, including idiopathic membranous nephropathy, type-2 diabetes, coronary heart disease, and chronic periodontitis (Chen and others 2010; Fan and others 2011; Zhang and others 2011). Functional genomic studies are needed verify the relevance of polymorphisms in the *IL-6* promoter to inflammatory markers in Han Chinese.

Our study has some potential limitations. First, we could not exclude the presence of previous asymptomatic AF in the control group, because these conclusions were based solely on the medical history of the interviews with the participants. Secondly, the absence of the assessment of serum IL-6 levels concordant with the *IL-6* −634C/G polymorphism may limit the outcomes. Finally, although all the study subjects were Han Chinese, and thus the possibility of ethnicity as a confounding factor could be excluded, the association of the *IL-6* −634C/G polymorphism and AF in other populations remains unknown and needs further study.

In conclusion, our data support that the *IL-6* −634C/G polymorphism is associated with AF, and the G allele has increased risk for AF in elderly Han Chinese patients with EH. Given the inherent limitations of case–control studies and the complex nature of genetic susceptibility for chronic degenerative diseases, the prospective and interventional clinical studies with a larger sample size are required to be conducted in individual ethnic groups to confirm our observations.

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Author Disclosure Statement

No competing financial interests exist.

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