ORIGINAL RESEARCH

# Significant Association Between *CAV1* Variant rs3807989 on 7p31 and Atrial Fibrillation in a Chinese Han Population

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***Background*—**Recent genome-wide association studies (GWAS) in European ancestry populations revealed several genomic loci for atrial fibrillation (AF). We previously replicated the 4q25 locus (*PITX2*) and 16q22 locus (*ZFHX3*) in the Chinese population, but not the *KCNN3* locus on 1q21. With single-nucleotide polymorphism rs3807989 in *CAV1* encoding caveolin-1, however, controversial results were reported in 2 Chinese replication studies.

***Methods and Results*—**Six remaining AF genetic loci from GWAS, including rs3807989/*CAV1*, rs593479/*PRRX1*, rs6479562/*C9orf3*, rs10824026/*SYNPO2L*, rs1152591/*SYNE2*, and rs7164883/*HCN4*, were analyzed in a Chinese Han population with 941 cases and 562 controls. Only rs3807989 showed significant association with AF ($P_{adj}=4.77\times10^{-5}$), and the finding was replicated in 2 other independent populations with 709 cases and 2175 controls, 463 cases and 644 controls, and the combined population with a total of 2113 cases and 3381 controls ($P_{adj}=2.20\times10^{-9}$; odds ratio [OR]=1.34 for major allele G). Meta-analysis, together with data from previous reports in Chinese and Japanese populations, also showed a significant association between rs3807989 and AF ($P=3.40\times10^{-4}$; OR=1.24 for allele G). We also found that rs3807989 showed a significant association with lone AF in 3 independent populations and in the combined population ($P_{adj}=3.85\times10^{-8}$; OR=1.43 for major allele G).

***Conclusions*—**The data in this study revealed a significant association between rs3807989 and AF in the Chinese Han population. Together with the findings that caveolin-1 interacts with potassium channels Kir2.1, KCNH2, and HCN4 and sodium channels Nav1.5 and Nav1.8, *CAV1* becomes a strong candidate susceptibility gene for AF across different ethnic populations. This study is the first to show a significant association between rs3807989 and lone AF. **(*J Am Heart Assoc*. 2015;4:e001980 doi: 10.1161/JAHA.115.001980)**

**Key Words:** atrial fibrillation • *CAV1* • genome-wide association studies (GWAS) • rs3807989 • single-nucleotide polymorphism

Atrial fibrillation (AF) is the most common form of sustained clinical cardiac arrhythmia, characterized by fast atrial rhythm and uncoordinated atrial mechanical activities.[1] AF is common and estimated to affect 0.4% to 1.0% of the general population.[1–3] AF accounts for 15% of strokes and increases risk of heart failure (HF) and sudden death by 2-fold.[4] Many risk factors, such as age, gender, hypertension (HTN), diabetes, obesity, HF, valvular heart disease, left ventricular (LV) dysfunction, and ischemic and structural heart disease can contribute to development of AF.[3,5,6] AF can occur in some patients who do not have any apparent structural heart diseases. This type of AF is referred to as lone AF.[1] Among all AF cases, nearly 30% are lone AF patients.[7,8] In mainland China, there are ≈10 million AF patients based on the estimation in 2008.[9–12]

Some genes have been found to be associated with familial AF by genetic analysis of families, for example, *SCN5A*, *KCNQ1*, *KCNE2*, *KCNJ2*, *KCNA5*, *KCNH2*, *NPPA*, and *NUP155*.[13–23] On the other hand, common sporadic AF is caused by genetic factors (susceptibility genes), environmental factors, and their interactions. Genome-wide association studies (GWAS) have identified several single-nucleotide polymorphisms (SNPs) associated with AF, such as rs2200733 near *PITX2*, rs7193343 and rs2106261 in *ZFHX3*,

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rs13376333 in *KCNN3*, rs3807989 in *CAV1*, and rs1152591 in *SYNE2*.[24–27] SNP rs3807989 in *CAV1* was previously reported to be associated with prolongation of the PR interval and AF in 2 GWAS in European ancestry populations in 2010.[28,29] After then, another meta-GWAS also revealed that rs3807989 was associated with AF.[30] Two independent studies were reported to investigate the association of rs3807989 with AF in the Chinese population; however, inconsistent results were obtained.[31,32] Li et al. failed to identify the association between rs3807989 and AF in a Chinese population with 839 cases and 1215 controls (*P* value after adjustment of covariates or $P_{adj}$=0.83; odds ratio [OR]=1.02 for minor allele A).[31] Liu et al., however, identified a significant association between rs3807989 and AF in a Chinese population with 597 cases and 996 controls ($P_{adj}=1.00\times10^{-3}$; OR=0.75 for minor allele A).[32] Owing to the reported controversial conclusions, further studies are needed to settle down the controversy about the association between rs3807989 and AF in the Chinese population. Therefore, we studied 3 independent Chinese case-control populations for AF with a total of 5494 subjects (2113 AF cases and 3381 controls) from GeneID. GeneID is a large GeneBank with more than 80 000 study subjects with cardiovascular diseases, such as coronary artery disease (CAD), AF, stroke, and diabetes mellitus (DM), and controls in China.[10,11,33–37] The 3 GeneID AF populations were used to explore the association of SNP rs3807989 with AF by both allelic and genotypic association analyses.

## Methods

### Study Subjects

Study subjects were from the Chinese GeneID database and of Han ethnic origin by self-description. This study was approved by the local ethics committees on human subject research. This study conformed to the guidelines set forth by the Declaration of Helsinki. Written informed consent was obtained from the participants.

In the present study, a total of 5494 subjects, including 2113 AF patients/cases and 3381 non-AF controls, were characterized (Table 1). Study subjects consisted of 3 independent populations: Population I, Population II, and Population III. There were 941 AF cases and 562 controls in Population I, 709 AF cases and 2175 controls in Population II, and 463 AF cases and 644 controls in Population III (Table 1). The number of lone AF cases in each population was 493, 320, and 326, respectively.

**Table 1.** Clinical and Demographic Characteristics of Study Subjects

| | Population I | | Population II | | Population III | | Population I+II+III (Combined) | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | AF (n=941) | Control (n=562) | AF (n=709) | Control (n=2175) | AF (n=463) | Control (n=644) | AF (n=2113) | Control (n=3381) |
| Male, n (%) | 571 (60.7) | 307 (54.6) | 405 (57.0) | 1293 (59.4) | 250 (54.0) | 303 (47.0) | 1226 (58.0) | 1903 (56.2) |
| *P* | 0.09 | | 0.25 | | 0.02 | | | |
| Age, y (mean±SD) | 67.1±14.4 | 61.4±11.3 | 65.0±13.6 | 49.3±14.8 | 64.6±10.4 | 62.2±8.8 | 65.4±13.1 | 53.7±14.6 |
| *P* | <0.001 | | <0.001 | | <0.001 | | | |
| Hypertension | 492 (52.3) | 271 (48.2) | 338 (47.7) | 447 (20.1) | 237 (51.2) | N/A | 1067 (50.5) | N/A |
| *P* | 0.13 | | <0.001 | | N/A | | | |
| DM | 121 (12.9) | 114 (20.3) | 78 (11.0) | 194 (8.9) | 61 (13.2) | N/A | 393 (18.6) | N/A |
| *P* | <0.001 | | 0.10 | | N/A | | | |
| CAD | 317 (33.7) | 143 (25.4) | 225 (31.7) | 212 (9.7) | 24 (5.2) | N/A | 633 (30.0) | N/A |
| *P* | <0.001 | | <0.001 | | N/A | | | |
| Lone AF, n (%) | 493 (52.4) | N/A | 320 (45.1) | N/A | 326 (70.4) | N/A | 960 (45.4) | N/A |
| Category | | | | | | | | |
| Paroxysmal, % | 753 (80.0) | N/A | 545 (76.9) | N/A | 344 (74.3) | N/A | 1642 (77.7) | N/A |
| Persistent, % | 138 (14.7) | N/A | 124 (17.5) | N/A | 105 (22.6) | N/A | 367 (17.4) | N/A |
| Longstanding persistent, % | 32 (3.4) | N/A | 16 (2.2) | N/A | 10 (2.2) | N/A | 58 (2.7) | N/A |
| Permanent, % | 18 (1.9) | N/A | 24 (3.4) | N/A | 4 (0.9) | N/A | 46 (2.2) | N/A |

Data are shown as mean±SD. We used chi-square ($\chi^2$) tests to compare frequencies of males, hypertension, DM (type II diabetes), and CAD between cases and controls in each population. We used a Student *t* test to compare the means of age in cases and controls in each population. AF indicates atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus.

Diagnosis of AF was based on standard criteria.[1] A patient with indistinct P waves, irregular RR intervals, and/or f waves on electrocardiograms (ECGs) was diagnosed as an AF patient. Patients with other types of cardiac arrhythmias, cardiomyopathies, and valvulopathies were excluded.[11] Exclusion criteria of lone AF included a history of CAD, a LV ejection fraction (LVEF) of <50%, significant valvular disease, and structural heart defects detected on echocardiography, as previously reported.[30] An "AF control" was an individual without arrhythmias, ischemic stroke, valvulopathies, and cardiomyopathies by ECGs, echocardiography, or magnetic resonance imaging/computed tomography.[11] The information of age, gender, and other relevant medical information, if present, were obtained from medical records.

## Isolation of Genomic DNA and Genotyping of SNPs

Human genomic DNA was extracted from peripheral blood samples using the Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI).

SNPs were genotyped using a Rotor-Gene 6000 High Resolution Melt system (Corbett Life Science, Concorde, NSW, Australia). A total of 25 μL of polymerase chain reaction (PCR) mixture for genotyping contained 1.5 mmol/L of $Mg^{2+}$, 0.2 mmol/L of dNTPs, 0.5 μmol/L of each primer, 25 ng of human genomic DNA template, 5 μmol/L of SYTO 9 green fluorescent, and 0.15 U of Taq DNA polymerase (TIANGEN, Beijing, China). PCR was performed on an ABI 9700 System (Applied Biosystems, Foster City, CA) with a thermal profile of 95°C for 5 minutes, 40 cycles of 95°C for 10 seconds, 59.4°C or other appropriate annealing temperatures for 10 seconds and 72°C for 15 seconds, and 72°C for 10 minutes. Primers for PCR are listed in Table 2. PCR products were directly genotyped using high-resolution melting (HRM) analysis on a Rotor-Gene 6000 System (Corbett Life Science, Australia) under standard protocols, with minor modifications.[33] Three positive controls for each genotype and a negative control of $ddH_2O$ were included during each run of HRM. Twenty samples were randomly selected for direct Sanger sequencing. Primers for sequencing are listed in Table 2. Sequencing results confirmed genotypes identified by HRM analysis.

## Statistical Analyses

Power analysis of each study population was conducted using the Power and Sample Size Calculations program (PS version 3.0.43). Hardy-Weinberg linkage disequilibrium analysis was

**Table 2.** Sequences for Primers Used of High-Resolution Melting Genotyping and Sequencing Analyses

| SNP | HRM Primers | Sequencing Primers |
|---|---|---|
| rs593479 | | |
| Forward primer | CCC CAG TCT GAT CCT CCT ACA | TCC CCA GTC TGA TCC TCC TAC A |
| Reverse primer | GGG GAT GGA TGG AAC AGA AA | GCA GGT GAG CCA GGA TAG AGA CT |
| rs3807989 | | |
| Forward primer | TCG CTG GCC CTT CTG TGG | ATC CCT CCT CTC TGT TCA AGT TC |
| Reverse primer | TGA TTC TTT TTT GTC CTC TGG TGT C | TGG CCT CAC GTG TTC ATT ATC |
| rs6479562 | | |
| Forward primer | CCC TCC ACG CTT TTT GTC ATA | GCC CCC TCC ACG CTT TTT GTC AT |
| Reverse primer | CCC GTG TTC AGT GTC CAG CT | TCG GGC AGC AGA GAT GTA TA |
| rs10824026 | | |
| Forward primer | CGG GGG AAA TGC AAA GTG T | CCA GCA GCA GAG ACC CCA GTG |
| Reverse primer | GGA TAC TGC CCC TAG CCT TC | CGG AGT TTC ACC AAG TTA TCT AG |
| rs1152591 | | |
| Forward primer | AAG CCC TAA ACC ACA GTA TCC A | TTC CAA GCC CTA AAC CAC AGT ATC |
| Reverse primer | CCT GGG AAC CTG ATC TTT TTA A | GGC CCC ACT CCA GAT TGT C |
| rs7164883 | | |
| Forward primer | ACC CCA CTT CTT GAC TTT TCT GA | AAA CCA CAG ATC AAC CCC ACT TC |
| Reverse primer | GGG CAA GTG TCC AGT GGT ATC | ATG CCA GCT CAC CTC CTC TTC |

HRM indicates high-resolution melting; SNP, single-nucleotide polymorphism.

performed with PLINK software (version 1.07) in each control population. Then, 2×2 Pearson chi-square ($\chi^2$) contingence tables were used for allelic association analysis, and 2×3 Pearson $\chi^2$ contingence tables were used for genotypic association analysis. Odds ratios (ORs) and corresponding 95% confidential intervals (CIs) were also calculated. Pearson $\chi^2$ tests and unpaired Student *t* tests were performed with SPSS (version 17.0; SPSS, Inc., Chicago, IL). For association analyses, we also performed multiple logistic regression analysis to adjust significant covariates of CAD, HTN, DM, and/or gender/age for AF using SPSS (version 17.0; SPSS, Inc.).

We performed a meta-analysis using Comprehensive Meta-Analysis software (version 2). For the meta-analysis, we included ORs and 95% CIs from previous studies involving Asian populations for SNP rs3807989. We then tested heterogeneity among different studies. Based on I-square ($I^2$) and *P* values, an appropriate model was selected for meta-analysis. When $I^2$<50% and *P*>0.05, the meta-analysis was performed under a fixed-effect model. When $I^2$>50% and *P*<0.05, the meta-analysis was performed under a random-effect model.

## Results

### Significant Allelic Association Between *CAV1* SNP rs3807989 and AF

GWAS in European ancestry populations have identified 10 major loci for AF.[30] We reported previously that genomic variants near *PITX2* on 4q25 and in *ZFHX3* were associated with AF in the Chinese Han population, but the association between SNP rs13376333 in *KCNN3* and AF was not replicated in the Chinese population.[10,11] Here, using a Chinese Han population consisting of 941 AF cases and 562 controls (Population I; Table 1), we assessed associations between AF with other GWAS SNPs identified in European ancestry populations, including SNP rs593479 located in *PRRX1*, SNP rs3807989 located in *CAV1*, SNP rs6479562 located in *C9orf3*, SNP rs10824026 located in *SYNPO2L*, SNP rs1152591 located in *SYNE2*, and SNP rs7164883 located in *HCN4*. SNP rs2040862 in *WNT8A* has only 1 genotype in the Chinese population (the NCBI SNP database; http://www.ncbi.nlm.nih.gov/snp/) and thus was not analyzed in our study. Genotypic frequencies for all SNPs in the control population did not deviate from Hardy-Weinberg equilibrium (*P*>0.01). The minor allele frequency (MAF) of each SNP was similar to the data for the Chinese Han population from the NCBI SNP database (http://www.ncbi.nlm.nih.gov/snp/) (Table 3). Only SNP rs3807989 in *CAV1* showed a significant association with AF ($P_{adj}=4.77\times10^{-5}$; OR=1.42), whereas other SNPs did not show a significant association with AF in the Chinese Han population ($P_{adj}$>0.05; Table 3). The major G allele of SNP rs3807989 is the risk allele in Chinese Han populations (Table 3).

To further validate the association of *CAV1* SNP rs3807989 and AF, we performed genetic association analysis in 2 other independent Chinese Han populations and in the large combined population. Populations II and III consisted of 709 AF cases and 2175 controls, and 463 AF cases and 644 controls, respectively (Table 1). Statistical power analysis showed that Populations II and III had a power of >90% and

**Table 3.** Allelic Association of 6 GWAS SNPs With AF in GeneID Population I

| Locus | SNP | Gene | Major/Minor Allele | MAF (Case/Control) | Expected MAF | Before Adjustment | | After Adjustment | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $P_{obs}$ | OR (95% CI) | $P_{adj}$ | OR (95% CI) |
| 1q24 | rs593479 | *PRRX1* | T/C | 0.385/0.404 | 0.442 | 0.31 | 1.08 (0.93 to 1.25) | 0.35 | 1.08 (0.92 to 1.26) |
| 7q31 | rs3807989 | *CAV1* | G/A | 0.245/0.313 | 0.298 | 6.64E-05 | 1.40 (1.18 to 1.65) | 4.77E-05 | 1.42 (1.20 to 1.68) |
| 9q22 | rs6479562 | *C9orf3* | G/A | 0.270/0.236 | 0.233 | 0.04 | 0.83 (0.70 to 0.99) | 0.11 | 0.87 (0.73 to 1.03) |
| 10q22 | rs10824026 | *SYNPO2L* | A/G | 0.404/0.375 | 0.372 | 0.12 | 1.13 (0.97 to 1.31) | 0.08 | 1.15 (0.98 to 1.34) |
| 14q23 | rs1152591 | *SYNE2* | C/T | 0.318/0.298 | 0.291 | 0.23 | 1.10 (0.94 to 1.29) | 0.15 | 1.13 (0.96 to 1.33) |
| 15q24 | rs7164883 | *HCN4* | A/G | 0.127/0.099 | 0.081 | 0.08 | 1.23 (0.98 to 1.56) | 0.07 | 1.25 (0.98 to 1.58) |

Expected MAF was based on the data for the Chinese Han population from the NCBI SNP database (http://www.ncbi.nlm.nih.gov/snp/). AF indicates atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; GWAS, genome-wide association studies; MAF, minor allele frequency; OR, odds ratio; $P_{adj}$, *P* value after adjusting for covariates of gender, age, CAD, hypertension, and DM by multiple logistic regression analysis using SPSS (version 17.0; SPSS, Inc., Chicago, IL); $P_{obs}$, observed *P* value for association by 2×2 contingence tables using PLINK (version 1.07); SNPs, single-nucleotide polymorphisms.

>85% to detect the association between SNP rs3807989 and AF.

Genotypes in control populations did not deviate from Hardy-Weinberg equilibrium ($P>0.01$). Significant allelic association was identified between SNP rs3807989 and AF in both replication populations ($P_{obs}=1.26\times10^{-5}$, OR=1.37 for major allele G in Population II; $P_{obs}=3.50\times10^{-3}$, OR=1.34 for major allele G in Population III; Table 4). After adjusting for covariates of CAD, HTN, DM, and/or gender/age, the association remained significant ($P_{adj}=2.42\times10^{-4}$, OR=1.35 for major allele G in Population II; $P_{adj}=3.03\times10^{-3}$, OR=1.35 for major allele G in Population III; Table 4). These data suggest that SNP rs3807989 in *CAV1* conferred a significant risk of sporadic AF in the Chinese Han population.

## Significant Association Between SNP rs3807989 and Lone AF

We also analyzed whether rs3807989 was associated with lone AF (ie, AF without any structural heart diseases). Exclusion criteria of lone AF included a history of CAD, an LVEF of <50%, significant valvular disease, and structural modifications of heart detected on echocardiography.[30] There are 493, 320, and 326 lone AF cases in Populations I, II, and III, respectively. A significant allelic association was identified between SNP rs3807989 and lone AF ($P_{obs}=5.87\times10^{-3}$, OR=1.36 for major allele G in Population I; $P_{obs}=2.95\times10^{-6}$, OR=1.64 for major allele G in Population II; $P_{obs}=7.30\times10^{-3}$, OR=1.35 for major allele G in Population III; Table 4). After adjusting for covariates of CAD, HTN, DM, and/or gender/age, the association remained significant ($P_{adj}=9.84\times10^{-3}$, OR=1.36 for major allele G in Population I; $P_{adj}=2.77\times10^{-5}$, OR=1.60 for major allele G in Population II; $P_{adj}=5.93\times10^{-3}$, OR=1.36 for major allele G in Population III; Table 4). These data suggest that SNP rs3807989 conferred a significant risk of lone AF in the Chinese Han population.

## Significant Allelic Association of SNP rs3807989 With AF and Lone AF in the Combined Chinese AF Population

To further assess the association between SNP rs3807989 and AF, we combined the 3 AF populations together. This generated the largest Chinese case-control association study population for AF with 2113 cases and 3381 controls and a large study population for lone AF with 1139 cases and 3381 controls to study rs3807989. The association between SNP rs3807989 and AF became much more significant in the combined AF population ($P_{obs}=2.19\times10^{-9}$, OR=1.31; $P_{adj}=2.20\times10^{-9}$, OR=1.34; Table 5). The same trend was observed in the combined population for lone AF as well ($P_{obs}=7.51\times10^{-8}$, OR=1.39; $P_{adj}=3.85\times10^{-8}$, OR=1.43; Table 5). Together, the data from 3 independent populations and from the combined population provided strong genetic evidence that major allele G of SNP rs3807989 played a significant risk role in AF and lone AF in the Chinese Han population.

## Significant Association of rs3807989 With AF by Meta-Analysis

Mining of GWAS data for AF in a Japanese population revealed a positive in silico association between SNP rs3807989 and AF.[30] Two previous studies investigated the association between SNP rs3807989 in *CAV1* and AF in Chinese Han populations; 1 failed to replicate the association,[31] but the other replicated the association.[32] We replicated the association in 3 independent Chinese populations. Thus, a

**Table 4.** Allelic Association of SNP rs3807989 With Both AF and Lone AF in Chinese Han Populations

| Study Population | Sample Size Case/Control | Major Allele | Frequency (Case/Control) | Before Adjustment | | After Adjustment | |
|---|---|---|---|---|---|---|---|
| | | | | $P_{obs}$ | OR (95% CI) | $P_{adj}$ | OR (95% CI) |
| AF | | | | | | | |
| Population I | 941/562 | G | 0.755/0.687 | 6.64E-05 | 1.40 (1.18 to 1.65) | 4.77E-05 | 1.42 (1.20 to 1.68) |
| Population II | 709/2175 | G | 0.781/0.723 | 1.26E-05 | 1.37 (1.19 to 1.58) | 2.42E-04 | 1.35 (1.15 to 1.58) |
| Population III | 463/644 | G | 0.767/0.711 | 3.50E-03 | 1.34 (1.10 to 1.62) | 3.03E-03 | 1.35 (1.11 to 1.64) |
| Lone AF | | | | | | | |
| Population I | 493/562 | G | 0.742/0.687 | 5.87E-03 | 1.36 (1.09 to 1.70) | 9.84E-03 | 1.36 (1.08 to 1.71) |
| Population II | 320/2175 | G | 0.809/0.723 | 2.95E-06 | 1.64 (1.33 to 2.01) | 2.77E-05 | 1.60 (1.29 to 2.00) |
| Population III | 326/644 | G | 0.768/0.711 | 7.30E-03 | 1.35 (1.08 to 1.68) | 5.93E-03 | 1.36 (1.09 to 1.69) |

AF indicates atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio; $P_{adj}$, *P* value after adjusting for covariates of age, gender, CAD, hypertension, and DM in Populations I and II or age and gender in Population III by multiple logistic regression analysis using SPSS (version 17.0; SPSS, Inc., Chicago, IL; $P_{obs}$, observed *P* value for association of the risk allele by 2×2 contingence tables using PLINK version 1.07; SNPs, single-nucleotide polymorphisms.

**Table 5.** Allelic Association of SNP rs3807989 With Both AF and Lone AF in the Combined Population

| Combined Population | Sample Size Case/Control | Major Allele | Frequency (Case/Control) | Before Adjustment | | After Adjustment | |
|---|---|---|---|---|---|---|---|
| | | | | $P_{obs}$ | OR (95% CI) | $P_{adj}$ | OR (95% CI) |
| AF | 2113/3381 | G | 0.766/0.714 | 2.19E-09 | 1.31 (1.20 to 1.43) | 2.20E-09 | 1.34 (1.22 to 1.47) |
| Lone AF | 1139/3381 | G | 0.769/0.714 | 7.51E-08 | 1.39 (1.23 to 1.56) | 3.85E-08 | 1.43 (1.26 to 1.62) |

AF indicates atrial fibrillation; CI, confidence interval; OR, odds ratio; $P_{adj}$, *P* value after adjusting for covariates of gender and age by multiple logistic regression analysis using SPSS (version 17.0; SPSS, Inc., Chicago, Il); $P_{obs}$, observed *P* value for association of the risk allele by 2×2 contingence tables using PLINK version 1.07; SNP, single-nucleotide polymorphism.

meta-analysis is needed to yield an ultimate conclusion about the association between SNP rs3807989 and AF in the East Asian populations. Heterogeneity analysis for the Asian populations with a *Q* test yielded $I^2$ of 67% and *P* of 0.028. Thus, a random-effect model is the best fit for meta-analysis. ORs and 95% CIs were obtained for minor allele A because only data for allele A were available from previously published reports.[30–32] Characteristics of the 4 Asian populations used for meta-analysis are shown in Table 6, and the entire population consisted of 4372 AF cases and 8942 controls. Meta-analysis showed a significant association between *CAV1* SNP rs3807989 and AF ($P=3.40\times10^{-4}$, OR=0.81 for minor allele A; ie, OR=1.24 for major allele G; Figure). These data suggest that SNP rs3807989 is significantly associated with AF in East Asian populations.

## Discussion

Three GWAS revealed that SNP rs3807989 in *CAV1* was associated with AF in the European ancestry populations. Two follow-up replication studies in Chinese Han populations, however, yielded inconsistent results, with 1 study showing a significant association between rs3807989 and AF and the other showing no association.[31,32] Owing to the controversy, further studies are needed. In this study, we report a highly significant association between SNP rs3807989 in *CAV1* and AF as well as lone AF in Chinese Han populations. In all 3 populations studied and the combined population with 2113 AF patients and 3381 controls, the major allele G of SNP rs3807989 is the risk allele for AF or lone AF, whereas the minor allele A plays a protective role. ORs ranged from 1.35 to 1.60 (Table 4). The OR for lone AF was greater than that for common AF (Table 4). To date, this study involves the largest population used to explore the association between SNP rs3807989 and AF or lone AF in Chinese Han populations. Our study is the first to show the significant association between SNP rs3807989 and lone AF.

Two previous studies investigated the association between SNP rs3807989 in *CAV1* and AF. Li et al. reported the first study that failed to identify the association with a population of 839 cases and 1215 controls ($P_{adj}=0.83$; OR=1.02 for minor allele A).[31] Subsequently, Liu et al., on the other hand, identified a significant association of rs3807989 with AF in a Chinese Han population with 597 cases and 996 controls ($P_{adj}=1.00\times10^{-3}$; OR=0.75 for minor allele A).[32] Exploration of GWAS data for AF in a Japanese population revealed a *P* value of $7.00\times10^{-5}$ for the association between SNP rs3807989 and AF.[30] Together with our results of a significant association between rs3807989 and AF in 3 independent populations and in the combined population with 2113 cases and 3381 controls (the largest population among all studies), we conclude that SNP rs3807989 is a significant susceptibility factor for AF. This conclusion is now supported by a meta-analysis showing a significant association between *CAV1* SNP rs3807989 and AF in East Asian populations (Figure). The previous failure to replicate could be a reflection of a smaller sample size.

SNP rs3807989 is located in the second intron of the *CAV1* gene that consisted of 3 exons. The *CAV1* gene encodes caveolin-1. Caveolin-1 is a key component of caveolae, 50- to

**Table 6.** Characteristics of the Populations Used for Meta-Analyses

| Studies | Population | Number (Case/Control) | Age, y (Case/Control) | Male, % (Case/Control) | Primary Outcome |
|---|---|---|---|---|---|
| Ellinor PT et al. (2012)[30] | Japan | 843/3350 | 67.3/52.4 | 68.7/54.4 | AF |
| Li et al. (2014)[31] | China | 839/1215 | 53/52 | 56.4/66.1 | AF |
| Liu et al. (2014)[32] | China | 597/996 | 58.4/59.0 | 66.5/67.7 | AF |
| GeneID* | China | 2113/3381 | 62.2/65.4 | 47.0/58.0 | AF |
| Total samples | | 4372/8942 | | | |

AF indicates atrial fibrillation.
*GeneID population is the combined replication cohort for AF in the present study.

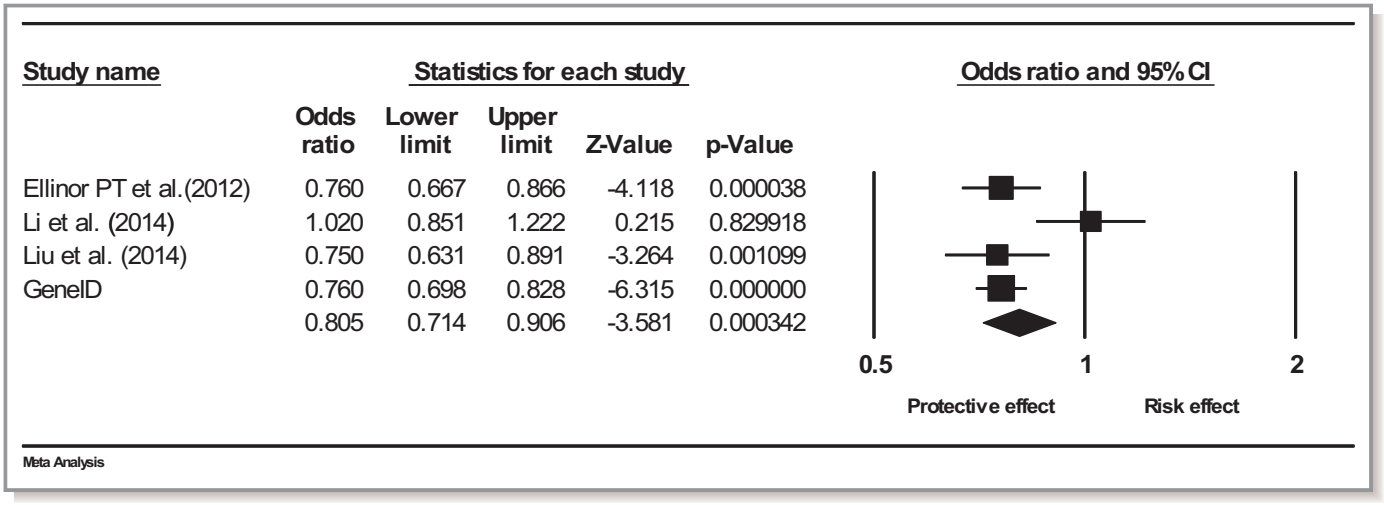


**Figure.** Forest plot of meta-analysis for SNP rs3807989 in Asian AF populations under a random-effect model. AF indicates atrial fibrillation; CI, confidence interval; SNP, single-nucleotide polymorphism.

100-nm plasma membrane vesicles involved in cell signaling, and helps assembly of caveolae as a coat and scaffolding protein.[38] Caveolin-1 has been shown to be expressed in cardiomyocytes.[39] Mutations and genomic variants in genes encoding ion channels are well known to cause AF. Caveolin-1 has been shown to interact with potassium channel subunit Kir2.1, which generates potassium current $I_{K1}$ with an important role in development of AF.[40] Caveolin-1 has also been shown to interact with cardiac potassium channels KCNH2[41] and HCN4.[42] Moreover, caveolin-1 also interacts with Nav1.8,[43] a voltage-gated sodium channel encoded by *SCN10A*, which was found to be associated with AF.[28,29] Caveolin-1 has also been shown to colocalize with Nav1.5,[44] another sodium channel encoded by *SCN5A* and associated with AF. Therefore, we speculate that SNP rs3807989 may increase risk of AF by altering the function of cardiac potassium channels Kir2.1, KCNH2, and/or HCN4 as well as sodium channels Nav1.5 and/or Nav1.8. Caveolin-1 was also found to play a role in TGF-β1 signaling.[45] Transforming growth factor beta 1 (TGF-β1) signaling plays an important role in atrial fibrosis,[46] a substrate for AF. Therefore, it is also possible that SNP rs3807989 may increase risk of AF by altering TGF-β1 signaling.

GWAS for AF in European ancestry populations successfully identified some common variants associated with AF, including 4q25 (*PITX2*), 16q22 (*ZFHX3*), 1q21 (*KCNN3*), 7q31 (*CAV1/CAV2*), 1q24 (*PRRX1*), 14q23 (*SYNE2*), 9q22 (*C9orf3*), 5q31 (*WNT8A*), 15q24 (*HCN4*), and 10q22 (*SYNPO2L*).[24–27,30] We replicated AF risk loci at 4q25 and 16q22 in the Chinese Han population in previous reports.[10,11] The association between GWAS variants at the *KCNN3* locus on 1q21 and AF failed to be replicated by our previous study using the Chinese GeneID population and by in silico mining of GWAS data for AF in the Japanese BioBank study,[10,30] suggesting that the *KCNN3* locus may confer risk of AF specifically in European ancestry populations (ie, a population-specific genetic risk factor). In this study, we assessed the remaining GWAS SNPs for an association with AF in the Chinese population. Surprisingly, all, except for *CAV1* SNP rs3807989, discussed above did not show any significant association with AF in the Chinese Han population (Table 3). Consistent with our results, the in silico replication study in the Japanese BioBank study also showed a negative replication for SNPs in *SYNPO2L*, *SYNE2*, and *HCN4* ($P>0.05$).[30] SNP rs12755237 in *PRRX1* proxy to GWAS SNP rs3903239 showed a *P* value of 0.013 in the Japanese AF GWAS database, and another SNP in *PRRX1*, rs593479, showed a *P* value of $2.4\times10^{-3}$ (before Bonferroni correction for 16 SNPs).[30] SNP rs356131 in *C9orf3* proxy to GWAS SNP rs10821415 showed a *P* value of 0.61 in the Japanese AF GWAS database, although another SNP in *C9orf3*, rs6479562, showed a *P* value of $4.2\times10^{-4}$.[30] Nevertheless, SNPs rs593479 and rs6479562 did not show a significant association with AF in the Chinese Han population with $P_{adj}$ of 0.35 and 0.11, respectively (Table 3). These data suggest that some genomic variants confer risk of AF across different ethnic backgrounds, that is, from European ancestry populations to East Asian populations (eg, *PITX2* and *ZFHX3* variants), whereas other variants confer risk of AF only in European ancestry populations (ie, not in Chinese or Japanese populations), indicating strong population heterogeneity in genetics of AF.

## Conclusions

In conclusion, we identified a significant association between SNP rs3807989 in *CAV1* with common sporadic AF in the Chinese Han population. Meta-analysis showed a significant association between SNP rs3807989 and AF in East Asian

populations. More importantly, for the first time, we found that SNP rs3807989 was also associated with lone AF. Future studies may focus on functional characterization of *CAV1* as a strong candidate susceptibility gene for AF.

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## Disclosures

None.

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