Original Article

# Insights into the genetic basis of *HMGB1* in atrial fibrillation in a Chinese Han population

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**Background:** Atrial fibrillation (AF) is the most common cardiac arrhythmia. High mobility group box 1 (HMGB1) has been demonstrated to be involved in AF, but the genetic relationship between them is not clear yet. Here, we investigated the genetic association between functional variants in *HMGB1* and AF in a Chinese Han population.

**Methods:** Two common variants (the promoter one rs1045411$^{T/C}$ and the 3'UTR one rs1412125$^{C/T}$) in *HMGB1* were selected and genotyped in 576 AF patients and 869 control subjects. Traditional risk factors, such as age, gender, the history of smoking, hypertension and diabetes mellitus, were adjusted as covariates using a logistic regression analysis (SPSS, v.21.0). The haplotypic analysis was performed using SPSS (v.21.0, Inc., Chicago, IL, USA).

**Results:** Under the allelic association analysis, neither rs1045411$^{T/C}$ nor rs1412125$^{C/T}$ was associated with AF with all P values >0.05; under the genotypic association analysis, the 3'UTR variant rs1045411$^{T}$ showed a marginally significant association with AF under the recessive model ($P_{adj}$=0.056, OR =0.42; 95% CI: 0.17–1.02). When divided the studied population by gender, we still found no significant association results between the selected variants and AF with P values more than 0.05; however, when divided the population into subgroups by the age onset of AF, we found that the 3'UTR variant rs1045411$^{T}$ was significantly associated with AF in the late-onset subgroup ($P_{adj}$=0.009, OR =11.1; 95% CI: 1.82–50.0).

**Conclusions:** The 3'UTR variant rs1045411$^{T/C}$ of *HMGB1* might influence the risk of late-onset AF in the Chinese Han population, which provides an important target factor for the prevention and treatment study of AF.

**Keywords:** Atrial fibrillation (AF); high mobility group box 1 (*HMGB1*); genetic association

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## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and profoundly increased the mortality, morbidity and healthy costs worldwide (1). In the past, traditional risk factors for AF, such as age, gender, smoking, hypertension and diabetes, have been illustrated fully and made a major contribution in the prevention and treatment of the disease (2-5). However, paroxysmal AF in young and middle-aged athletes was discovered with no traditional risk factors, which might indicate other factors with genetic basis involved in AF (6). Though, genomewide association studies have identified at least 30 genetic risk loci for AF, and explored lots of new molecular mechanisms for the development of AF (7-14), the exact pathology of AF still

remains largely to be explained. Therefore, other studies, such as candidate gene association analysis, might be an important way to investigate the genetic basis of AF.

High mobility group box 1 (HMGB1) protein is a multifunctional redox sensitive protein and act both as a nuclear factor and a secreted protein (15-17). In 2009, Hu *et al.* reported that the serum level of HMGB1 was markedly increased with the severity of coronary artery stenosis in the patients of stable angina pectoris, which indicated that HMGB1 might involve in the development of coronary artery diseases, and the latter is one of the major cause for AF (18). In 2010, the same team studied in rats that, HMGB1 might improve the myocardial ischemia by decreasing the cell viability and promoting the apoptosis of neonatal myocytes, of which the latter might increase the incidence of AF (19). In the same year, Giallauria *et al.* reported that the serum HMGB1 levels were highly correlated with the autonomic dysfunction expressed by post-exercise slower HRR in post-infarction patients, which might increase the incidence of adverse cardiovascular events, such as AF and VF (20). In 2011, another research team found that the serum level of HMGB1 in AF patients was much higher than that of the control subjects (21). In 2013, Wu *et al.* studied that HMGB1 might improve the development of AF by increasing the oxidative stress in the patients (22). These evidences above indicated that there was a strong relationship between HMGB1 and AF, but the exact relationship between them are not clear yet.

Therefore, we investigated the genetic basis of HMGB1 in AF: we selected the variants locus in the regulatory region of *HMGB1*, and studied the genetic association between the selected variants and AF in a Chinese Han population.

## Methods

### *Study population*

In total, 576 AF cases and 869 controls were selected from the People's Hospital of Yichang Center (Hubei, China). AF cases were diagnosed by cardiologists according to the guidelines (23). The control subjects were selected from the individuals with normal electrocardiogram and have no history of AF or any other cardiac arrhythmias. All of the individuals with type 1 diabetes, congenital heart disease, and heavy renal or hepatic diseases were excluded from this study. The control subjects with rheumatic autoimmune disease, tumor or stroke were also excluded from this study. The clinical characteristics, such as age, gender, history of smoking status, hypertension and diabetes mellitus, were obtained by direct interviews and medical record reviews.

This study was approved by the Ethics Committee of People's Hospital of Yichang Center, and conformed to the ethical principles set forth by the Declaration of Helsinki. The informed consent was obtained from all the participants.

### *SNP selection*

We selected the tag variants as following rules: first, the minor allele frequency (MAF) of the SNPs was greater than 0.05; second, the variants were given priorities, if they were previously reported functional variants or predicted potential functional sites by bioinformatics (Promoter, Genevar) (24). Two SNPs, rs1045411$^{T/C}$ nor rs1412125$^{C/T}$, were selected according to the rules above. Rs1412125$^{C/T}$ locus in the promoter region of *HMGB1* and rs1045411$^{T/C}$ locus in the 3'UTR region of *HMGB1*, of which both might regulate the gene expression of *HMGB1*.

### *Genotyping*

We extracted the DNA samples from the peripheral blood of the studied population, following the standard process of the kit (the Wizard Genomic DNA Purification Kit, Promega Corporation, Madison, WI). Genotyping was performed with the selected SNPs using a Rotor Gene 6000 High-Resolution Melt (HRM) system (Corbett Life Science, Concorde, NSW, Australia). The PCR reaction system was in a total of 25 μL PCR volume containing 1 μL of LC Green dye, 5 pmol of each primer, 25 ng of genomic DNA, 2.5 μL of 10× PCR buffer with 1.5 mmol/L $MgCl_2$, 5 mmol deoxynucleotide triphosphates, and 1 unit of Taq polymerase. Genotyping results were confirmed by Sanger sequencing.

### *Statistical analysis*

Hardy-Weinberg disequilibrium tests were carried out for the selected SNPs in the control subjects using PLINK software version 1.07. The allelic and genotypic association analysis, as well as the odds ratio (OR) and 95% confidence interval (CI), were performed by the conduction of Pearson's chi-square tests of 2×2 or 2×3 contingency tables (v.21.0, SPSS, Inc., Chicago, IL, USA). Traditional risk factors, such as age, gender, the history of smoking, hypertension and diabetes mellitus, were adjusted as

 

covariates using a logistic regression analysis (SPSS, v.21.0). The haplotypic analysis was performed using SPSS (v.21.0, Inc., Chicago, IL, USA).

## Results

### *Population characteristics*

The characteristics of the studied subjects were illustrated in *Table 1*. Subjects in the AF case group were much older than those in the control group. AF cases also showed higher prevalence of male percent, hypertension and diabetes mellitus. However, the prevalence of the smoking status, which is also an important traditional risk factor for AF, were not significantly different between the AF case group and the control group.

### *Association analysis between the selected SNPs of HMGB1 and AF in a Chinese Han population*

Both of the two selected variants (rs1045411$^{T/C}$ nor rs1412125$^{C/T}$) in *HMGB1* passed the Hardy-Weinberg disequilibrium tests in the control subjects (P>0.05) (*Table 2*). Under the allelic association analysis, rs1045411$^{T}$ was not associated with AF neither before nor after the adjustment of the traditional risk factors in the Chinese Han population ($P_{obs}$=0.520, $P_{adj}$=0.839, OR =1.03; 95% CI: 0.77–1.38); rs1412125$^{C}$ also showed no association with AF neither before nor after the traditional risk factors for AF in the Chinese Han population with all P values more than 0.1 ($P_{obs}$=0.982, $P_{adj}$=0.715, OR =0.95; 95% CI: 0.73–1.24) (*Table 2*). Under the genotypic association analysis, rs1045411$^{T/C}$ showed a marginally significant association result with AF in the recessive model with adjusted p value of 0.056 (OR =0.42; 95% CI: 0.17–1.02); rs1412125$^{C/T}$ still showed no significant association with AF with all P values more than 0.1 in all the models (additive, dominant and recessive models) (*Table 3*). Under the haplotypic association analysis, we still found that the distribution frequency of the haplotypes had no significant difference between the AF cases and the controls with all P values more than 0.1 (*Table 4*).

**Table 1** The characteristic of the study population

| Characteristic | AF (n=576) | Control (n=869) | P |
|---|---|---|---|
| Age (years) | 66.56±10.87 | 42.28±11.60 | $<10^{-6}$ |
| Male (%) | 52.47 | 40.10 | $4.0\times<10^{-5}$ |
| Smoking (%) | 11.05 | 13.72 | 0.128 |
| Hypertension (%) | 39.36 | 14.24 | $<10^{-6}$ |
| DM | 9.90 | 3.65 | $<10^{-6}$ |

The data are shown as the mean ± SD. Categorical data, including gender, smoking status and other data, were tested using chi-square tests, and the measurement data age was tested using *t*-tests between the cases and controls in each population. Age for the case group is the age at diagnosis; age for the control group is the age at enrollment. AF, atrial fibrillation; DM, diabetes mellitus.

### *Association analysis between the selected variants and AF in the gender subgroup*

We classified all the studied populations by gender and then investigated the association between the two SNPs (rs1045411$^{T/C}$ nor rs1412125$^{C/T}$) and AF in different gender subgroups. Under the allelic association analysis, none of the two variants showed significant association with AF in the two gender subgroups with all P values more than 0.1 (*Table 5*). Under the genotypic association analysis, rs1045411$^{T/C}$ showed marginally significant association with AF in the male subgroup in recessive model ($P_{obs}$=0.065) (*Table 5*). However, after adjusted the traditional risk factors for AF, this association result did not remain with the adjusted P value of 0.104 (OR =0.36; 95% CI: 0.11–1.23) (*Table 5*).

**Table 2** Allelic association analysis between the variants in *HMGB1* and AF in the Chinese Han population

| SNP-allele (N, case/control) | Frequency | | $P_{hwb}$ | $P_{obs}$ | $P_{adj}$ | OR (95% CI) |
|---|---|---|---|---|---|---|
| | Case | Control | | | | |
| Rs1045411$^{T/C}$ (1,152/1,738) | 0.203/0.797 | 0.194/0.806 | 0.705 | 0.520 | 0.839 | 1.03 (0.77–1.38) |
| Rs1412125$^{C/T}$ (1,152/1,738) | 0.271/0.729 | 0.272/0.728 | 0.595 | 0.982 | 0.715 | 0.95 (0.73–1.24) |

SNP, single nucleotide polymorphism; AF, atrial fibrillation; MAF, minor allele frequency; $P_{obs}$, observed P value; $P_{hwe}$, P value of the Hardy-Weinberg equilibrium tests; $P_{adj}$, P value after adjusting for age, gender, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment.

**Table 3** Genotypic association of the selected variants in *HMGB1* with AF in the Chinese Han population

| SNP-allele | Model | N | | $P_{obs}$ | $P_{adj}$ | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Case | Control | | | |
| Rs1045411$^{T}$ | ADD | 24/305/540 | 23/177/376 | 0.127 | 0.834 | 0.97 (0.72–1.31) |
| | DOM | 329/540 | 200/376 | 0.225 | 0.624 | 1.09 (0.77–1.54) |
| | REC | 24/845 | 23/553 | 0.196 | 0.056* | 0.42 (0.17–1.02) |
| Rs1412125$^{C}$ | ADD | 73/325/471 | 40/233/303 | 0.379 | 0.722 | 0.95 (0.74–1.23) |
| | DOM | 398/471 | 273/303 | 0.551 | 0.756 | 1.05 (0.76–1.47) |
| | REC | 73/796 | 40/536 | 0.313 | 0.163 | 0.65 (0.35–1.19) |

*, P<0.1. $P_{obs,}$ observed P value; $P_{adj,}$ P value adjusted for age, gender, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment; ADD, additive model, rs145411_TT/CT/CC, rs1412125_CC/TC/TT; DOM, dominant model, rs145411_TT+CT/CC, rs1412125_CC+TC/TT; REC, recessive model, rs145411_TT/CT+CC, rs1412125_CC/TC+TT.

**Table 4** Haplotypic association analysis of *HMGB1* with AF in the Chinese Han population

| Gene | Haplotype | N (%) | | $P_{obs}$ | $P_{adj}$ | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Case (n=1,736) | Control (n=1,152) | | | |
| *HMGB1* (rs1045411$^{T/C}$-rs1412125$^{C/T}$) | T-C | 62 (3.57) | 47 (4.08) | 0.583 | 0.377 | 1.31 (0.72–2.38) |
| | T-T | 291 (16.76) | 176 (15.28) | 0.282 | 0.654 | 0.93 (0.66–1.29) |
| | C-C | 409 (23.56) | 266 (23.09) | 0.641 | 0.402 | 0.89 (0.66–1.18) |
| | C-T | 974 (56.11) | 663 (57.55) | – | – | – |

$P_{obs}$, observed P value; $P_{adj}$, P value adjusted for age, gender, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment.

**Table 5** Association analysis of the SNPs in *HMGB1* with AF in the gender subgroups

| SNP-allele | Model | Male (N=687) | | | Female (N=758) | | |
|---|---|---|---|---|---|---|---|
| | | $P_{obs}$ | $P_{adj}$ | OR (95% CI) | $P_{obs}$ | $P_{adj}$ | OR (95% CI) |
| Rs1045411$^{T}$ | Allele | 0.944 | 0.300 | 1.25 (0.82–1.89) | 0.453 | 0.470 | 0.86 (0.57–1.30) |
| | ADD | 0.109 | 0.295 | 0.80 (0.52–1.22) | 0.652 | 0.464 | 1.17 (0.77–1.79) |
| | DOM | 0.568 | 0.570 | 0.87 (0.53–1.42) | 0.382 | 0.235 | 1.34 (0.83–2.19) |
| | REC | 0.065 | 0.104 | 0.36 (0.11–1.23) | 0.947 | 0.345 | 0.53 (0.14–1.97) |
| Rs1412125$^{C}$ | Allele | 0.494 | 0.660 | 1.09 (0.75–1.59) | 0.467 | 0.352 | 0.84 (0.59–1.21) |
| | ADD | 0.102 | 0.666 | 1.09 (0.75–1.57) | 0.784 | 0.358 | 0.85 (0.59–1.21) |
| | DOM | 0.156 | 0.288 | 1.30 (0.80–2.09) | 0.565 | 0.554 | 0.87 (0.55–1.38) |
| | REC | 0.275 | 0.356 | 0.65 (0.27–1.61) | 0.576 | 0.288 | 0.63 (0.27–1.47) |

SNP, single nucleotide polymorphism; $P_{obs}$, observed P value; $P_{adj}$, P value after adjusting for age, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment; ADD, additive model, rs145411_TT/CT/CC, rs1412125_CC/TC/TT; DOM, dominant model, rs145411_TT+CT/CC, rs1412125_CC+TC/TT; REC, recessive model, rs145411_TT/CT+CC, rs1412125_CC/TC+TT.

**Table 6** Association analysis of the SNPs in *HMGB1* with AF in the onset age subgroups

| SNP-allele | Model | Early-onset | | | Late-onset | | |
|---|---|---|---|---|---|---|---|
| | | $P_{obs}$ | $P_{adj}$ | OR (95% CI) | $P_{obs}$ | $P_{adj}$ | OR (95% CI) |
| $Rs1045411^{T}$ | Allele | 0.978 | 0.917 | 1.02 (0.76–1.36) | 0.324 | 0.618 | 1.17 (0.63–2.20) |
| | ADD | 0.357 | 0.912 | 0.98 (0.73–1.32) | 0.125 | 0.594 | 0.83 (0.42–1.64) |
| | DOM | 0.648 | 0.592 | 1.10 (0.78–1.55) | 0.129 | 0.823 | 1.09 (0.51–2.32) |
| | REC | 0.230 | 0.093# | 2.17 (0.88–5.56) | 0.347 | 0.009* | 11.1 (1.82–50.0) |
| $Rs1412125^{C}$ | Allele | 0.833 | 0.780 | 0.96 (0.74–1.25) | 0.885 | 0.430 | 0.80 (0.45–1.40) |
| | ADD | 0.095 | 0.789 | 0.97 (0.75–1.25) | 0.932 | 0.385 | 0.76 (0.41–1.42) |
| | DOM | 0.152 | 0.128 | 0.63 (0.34–1.14) | 0.721 | 0.501 | 0.55 (0.10–3.11) |
| | REC | 0.277 | 0.620 | 1.09 (0.78–1.52) | 0.999 | 0.471 | 0.76 (0.37–1.59) |

#, P<0.1; *, P<0.05. SNP, single nucleotide polymorphism; $P_{obs}$, observed P value; $P_{adj}$, P value after adjusting for age, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment; ADD, additive model, rs145411_TT/CT/CC, rs1412125_CC/TC/TT; DOM, dominant model, rs145411_TT+CT/CC, rs1412125_CC+TC/TT; REC, recessive model, rs145411_TT/CT+CC, rs1412125_CC/TC+TT.

$Rs1412125^{C/T}$ again showed no association with AF under the genotypic association analysis neither in the male subgroup nor in the female subgroup in any models with all P values more than 0.1 (*Table 5*). Under the haplotypic association analysis, the combination type $rs1045411^{T}$-$rs1412125^{T}$ was marginally associated with AF [($P_{adj}$=0.097, OR =0.67; 95% CI: 0.42–1.07) (*Table S1*); and $rs1045411^{C}$-$rs1412125^{C}$ also showed marginally association with AF with an adjusted P value of 0.086 (OR =0.71; 95% CI: 0.48–1.05) (*Table S1*)].

### *Association analysis between the selected variants and AF in the age onset subgroup*

We divided the AF case population into two subgroups by the age onset of AF and investigated the association between the two SNPs ($rs1045411^{T/C}$ nor $rs1412125^{C/T}$) and AF in different age onset subgroup. Patients with the age onset of AF less than 65 years were defined as the early-onset AF subgroup, and the other patients were defined as the late-onset AF subgroup. Under the allelic association analysis, no significant association results were found between the two SNPs and AF neither in the early-onset AF subgroup nor in the late-onset AF subgroup with all P values more than 0.1 (*Table 6*). Under the genotypic association analysis, $rs1045411^{T}$ showed marginally significant association with AF in the early-onset subgroup, and highly significant association with AF in the late-onset subgroup (early-onset, $P_{adj}$=0.093, OR =0.46; 95% CI: 0.18–1.14; late-onset, $P_{adj}$=0.009, OR =11.1; 95% CI: 1.82–50.0) (*Table 6*); while $rs1412125^{C}$ showed no significant association with AF neither in the early-onset subgroup nor in the late-onset subgroup. In addition, the haplotypic association analysis showed no significant association results neither in the early-onset subgroup, nor in the late-onset subgroup with all P values more than 0.1 (*Table S2*).

## Discussion

In this study, we investigated the genetic basis of *HMGB1* in AF in a Chinese Han population. In total study population, the promoter variant $rs1412125^{C/T}$ was not associated with AF neither under the allelic association analysis, nor under the genotypic association analysis; the 3'UTR variant $rs1045411^{T/C}$ in *HMGB1* was not associated with AF under the allelic association analysis, but under the genotypic association analysis, $rs1045411^{T}$ was marginally associated with AF in the recessive model; the haplotypes of the two SNPs ($rs1045411^{T/C}$ nor $rs1412125^{C/T}$) in *HMGB1* were not associated with AF. In the gender subgroup, neither $rs1412125^{C/T}$ nor $rs1045411^{T/C}$ showed significant association with AF under the allelic or genotypic association analysis; the combination types of $rs1045411^{T}$-$rs1412125^{T}$ and $rs1045411^{C}$-$rs1412125^{C}$ showed marginally association with AF under the haplotypic association analysis in the female subgroup. In the age onset subgroups, $rs1412125^{C}$ was not associated with AF in any subgroup;

 

rs1045411$^{T}$ was marginally associated with early onset AF and significantly associated with late-onset AF under the genotypic association analysis in the recessive model; the haplotypic association analysis showed none significant association results in any subgroups.

*HMGB1* is a highly conserved chromatin protein and binds with DNA and regulates other genes' expression in the nucleus. It can also act as proinflammatory cytokine, which could be released by necrotic or damaged cells and activated immune cells, such as macrophages and monocytes (15,25). Researchers have reported that the serum levels of HMGB1 were increased much higher in the patients with inflammatory diseases, such as endotoxemia, sepsis, reperfusion injury, acute lung injury or autoimmune disease, myocardial ischemia, acute coronary syndrome and AF (15,18,19,21,26-28). In 2012, Hu *et al.* review that the HMGB1 might participate in the development of AF, by promoting oxidative stress, matrix metalloproteinase-9 upregulation and activation or the atrial structural remodeling (18-21,29). In 2015, Qu *et al.* reported that the intron variant of *HMGB1*, rs2249825, was associated with postoperative AF after coronary artery bypass grafting (CABG) under cardiopulmonary bypass (CPB) in a Chinese Han population (30). In above, *HMGB1* might play an important role in the development of AF and might be an important candidate gene for the risk of AF.

In this study, we selected two common variants located in the regulatory region of *HMGB1*, the promoter variant rs1412125$^{C/T}$ and the 3'UTR variant rs1045411$^{T/C}$, to test the association between the two variants in *HMGB1* and AF in a Chinese Han population. In 2016, Bao *et al.* first confirmed that the variant rs1045411, which is in close proximity to the microRNA (hsa-miR-505) binding site in the 3'UTR region of *HMGB1* gene, could significantly influence the mRNA expression of HMGB1 in gastric cancer tissues and two tumor cell lines (SGC-7901 and HEK-293T cell lines) (31-33). In 2017, Lin *et al.* also determined that the 3'-UTR SNP rs1045411$^{T/C}$ could alter the mRNA stability of HMGB1 and then increase risk to squamous cell carcinoma (OSCC) (34). In above, we might conclude that rs1045411$^{T/C}$ might be an important expression quantitative trait loci (e-QTL) for *HMGB1*. In recent years, lots of researchers discovered that the e-QTLs, which were variants regulated the expression of the genes, had the population heterogeneity, the tissue cell specificity and influence the risk of disease under different conditions (35,36). In our study, we found that rs1045411$^{T/C}$ significantly contributed to the risk of late onset AF, which indicated that rs1045411$^{T/C}$ might just be the e-QTL for *HMGB1* in the old patients.

In 2014, Wang *et al.* reported that rs1412125$^{C/T}$ and rs2249825$^{G/C}$ in *HMGB1* were associated with platinum-based chemotherapy responses in Chinese lung cancer patients, which indicated that the two variants (rs1412125$^{C/T}$ and rs2249825$^{G/C}$) in *HMGB1* might be important biomarkers for predicting the efficacy of platinum-based chemotherapy (37). In 2016, Wu *et al.* discovered that rs1412125$^{C/T}$ and rs2249825$^{G/C}$ in HMGB1 were associated with susceptible to the development of cervical invasive cancer in Taiwanese Women in the Chinese population (38); another team reported that the promoter variant rs1412125$^{C/T}$ in HMGB1 was associated with hepatocellular carcinoma (HCC) in Taiwan, which indicated that rs1412125$^{C/T}$ might be a genetic risk factor for HCC in the Chinese population (39). Here, we didn't find the association between the promoter variant rs1412125$^{C/T}$ in HMGB1 and AF, which indicated that rs1412125$^{C/T}$ was not a genetic risk factor for AF. In addition, we didn't select the variant rs2249825$^{G/C}$ because of its locus in the intron region of HMGB1, which might have no function in regulating of HMGB1 expression and might not be a functional risk variant for any diseases.

## Conclusions

Here, we might conclude that HMGB1 might be an important causal factor for the development of AF, and rs1412125$^{C/T}$ might be an important genetic risk factor for AF. All of these evidences provide important information in the study of treatment and prevention for AF. Further studies with larger sample size, functional study of HMGB1 in older subjects and interaction with other genes or microRNAs are needed to confirm our results.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cdt.2019.12.07). The authors have no conflicts of interest to declare.

 

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of People's Hospital of Yichang Center, and conformed to the ethical principles set forth by the Declaration of Helsinki. The informed consent was obtained from all the participants.



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## Supplementary

**Table S1** Haplotypic association analysis of *HMGB1* with AF in the gender subgroups

| Gene | Haplotype | Male | | Female | |
|---|---|---|---|---|---|
| | | $P_{adj}$ | OR (95% CI) | $P_{adj}$ | OR (95% CI) |
| *HMGB1* ($rs1045411^{T/C}$-$rs1412125^{C/T}$) | T-C | 0.615 | 1.23 (0.54–2.80) | 0.446 | 1.41 (0.58–3.40) |
| | T-T | 0.265 | 1.31 (0.82–2.11) | 0.097* | 0.67 (0.42–1.07) |
| | C-C | 0.538 | 1.14 (0.75–1.73) | 0.086* | 0.71 (0.48–1.05) |
| | C-T | – | – | – | – |

*, P<0.1. $P_{obs}$, observed P value; $P_{adj}$, P value adjusted for age, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment.

**Table S2** Haplotypic association analysis of *HMGB1* with AF in the onset age subgroups

| Gene | Haplotype | Early onset | | Lately onset | |
|---|---|---|---|---|---|
| | | $P_{adj}$ | OR (95% CI) | $P_{adj}$ | OR (95% CI) |
| *HMGB1* ($rs1045411^{T/C}$-$rs1412125^{C/T}$) | T-C | 0.519 | 1.22 (0.67–2.20) | 0.138 | 2.79 (0.72–10.8) |
| | T-T | 0.691 | 0.93 (0.67–1.31) | 0.646 | 0.85 (0.41–1.73) |
| | C-C | 0.511 | 0.91 (0.68–1.21) | 0.182 | 0.66 (0.35–1.22) |
| | C-T | – | – | – | – |

$P_{obs}$, observed P value; $P_{adj}$, P value adjusted for age, gender, hypertension, diabetes mellitus and smoking history; OR, odds ratio after the adjustment.