Genomic Variants in NEURL, *GJA1* and *CUX2* Signifcantly Increase Genetic Susceptibility to Atrial Fibrillation

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Abstract

Atrial fbrillation (AF) is the most common arrhythmia. In 2014, two new meta-GWAS identifed 5 AF loci, including the NEURL locus, *GJA1* locus, *CAND2* locus, and *TBX5* locus in the European ancestry populations and the NEURL locus and *CUX2* locus in a Japanese population. The *TBX5* locus for AF was reported by us in 2013 in the Chinese population. Here we assessed the association between AF and SNPs in the NEURL, *GJA1*, *CAND2* and *CUX2* loci in the Chinese Han population. We carried out a large case-control association study with 1,164 AF patients and 1,460 controls. Signifcant allelic and genotypic associations were identifed between NEURL variant rs6584555 and *GJA1* variant rs13216675 and AF. Signifcant genotypic association was found between *CUX2* SNP rs6490029 and AF. No association was found between *CAND2* variant rs4642101 and AF, which may be due to an insufcient power of the sample size for rs4642101. Together with our previous fndings, seven of ffteen AF loci (<50%) identifed by GWAS in the European ancestry populations conferred susceptibility to AF in the Chinese population, and explained approximately 14.5% of AF heritability. On the other hand, two AF loci identifed in the Japanese population were both replicated in the Chinese population.

Result

Table 1. Clinical and demographical characteristics of study subjects.

Characteristics	AF Cases (n=1,164)	Controls (n=1,460)	*P**
Age (years, mean±SD)	61.27±11.33	63.8±13.54	<0.01
Male (%)	46.37%	42.18%	0.03
Coronary artery disease (CAD) (%)	24.32%	33.60%	<0.01
Hypertension (HTN) (%)	44.31%	48.62%	0.14
Type 2 diabetes (DM) (%)	14.86%	14.26%	0.31

Data are shown as mean +/- standard deviation (SD) for quantitative variables and percentage (%) for qualitative variables.
*The differences between cases and controls for qualitative variables such as gender, hypertension, type 2 diabetes and CAD were analyzed by a Chi-square (χ^2) test. The difference for quantitative variables such as means of age was analyzed with a student *t* test.
AF, atrial fibrillation.

Table 2. Allelic association analysis between rs4642101, rs13216675, rs6584555 and rs6490029 and AF in the Chinese Han population.

SNP	Chromosomal Position (hg19)	P_{hwe}	Risk Allele	Risk Allele Frequency (cases vs. controls)	Without Adjustment		After Adjustment		Bonferroni correction
					P_{obs}	*OR (95%CI)*	P_{adj}	*OR (95%CI)*	*P*
rs4642101 (*CAND2*)	Chr3:12842223	0.15	G	0.29/0.28	0.23	1.09 (0.95-1.24)	0.19	0.9 (0.79-1.05)	0.57
rs13216675 (near the *GJA1*)	Chr6: 122452329	0.03	T	0.66/0.61	3.9×10^{-3}	1.2 (1.06-1.37)	0.01	1.19 (1.04-1.35)	0.04
rs6584555 (*NEURL*)	Chr10:105299611	0.08	C	0.18/0.14	5.08×10^{-5}	1.38 (1.18-1.62)	9.06×10^{-5}	1.39 (1.18-1.64)	3.62×10^{-4}
rs6490029 (*CUX2*)	Chr12:111698457	0.10	A	0.74/0.72	0.22	0.92 (0.8-1.1)	0.54	1.05 (0.90-1.20)	0.95

P_{hwe}, *P* value for Hardy-Weinberg equilibrium (HWE) tests using PLINK version 1.07 in controls;
P_{obs}, *P* value for association before adjusting for covariates by 2 x 2 contingence table χ^2 tests using PLINK version 1.07;
P_{adj}, *P* value for association after adjusting for covariates of sex, age, HTN, CAD and DM by multiple logistic regression analysis using SPSS v17.0;
OR, odds ratio;
95% CI, 95% confidential interval.

Table 3. Genotypic association analysis between rs4642101, rs6584555, rs13216675 and rs6490029 and AF under three different genetic models.

Model*	Genotypes (AA/AB/BB)		Without Adjustment		Adjustment		Bonferroni correction
	Cases	Controls	P_{obs}	*OR (95%CI)*	P_{adj}	*OR (95%CI)*	*P*
rs4642101							
Additive	502/392/95	620/449/100	0.49	n.a	0.18	0.91 (0.8-1.04)	0.55
Dominant	502/487	620/549	0.29	1.10 (0.93-1.30)	0.26	0.9 (0.76-1.1)	0.70
Recessive	894/95	1069/100	0.35	1.14 (0.86-1.53)	0.27	0.85 (0.62-1.14)	0.72
rs13216675							
Additive	124/471/460	177/476/430	6.72×10^{-3}	n.a	0.01	1.19 (1.04-1.35)	0.04
Dominant	124/931	177/906	2.28×10^{-3}	1.47 (1.15-1.88)	3.04×10^{-3}	1.49 (1.14-1.92)	0.01
Recessive	595/460	653/430	0.07	1.17 (0.99-1.4)	0.14	0.87 (0.72-1.05)	0.45
rs6584555							
Additive	737/294/50	952/290/32	4.03×10^{-4}	n.a	4.85×10^{-5}	1.41 (1.19-1.67)	1.94×10^{-4}
Dominant	737/344	952/322	4.38×10^{-4}	1.38 (1.15-1.65)	4.26×10^{-4}	1.43 (1.16-1.72)	1.70×10^{-3}
Recessive	1031/50	1242/32	5.3×10^{-3}	1.89 (1.2-2.96)	1.51×10^{-3}	2.32 (1.37-3.85)	6.03×10^{-3}
rs6490029							
Additive	58/412/530	97/423/578	0.02	n.a	0.54	0.96 (0.83-1.1)	0.95
Dominant	58/942	97/1001	7.97×10^{-3}	1.57(1.12-2.2)	8.28×10^{-3}	1.61(1.12-2.27)	0.04
Recessive	470/530	520/578	0.87	1.01(0.86-1.2)	0.65	1.04 (0.87-1.25)	0.96

*Additive model = AA/AB/BB; dominant model = AA+AB/BB; recessive model = AA/AB+BB;
P_{obs}, *P* value for association before adjusting for covariates by 2 x 2 contingence table χ^2 test using PLINK version 1.07;
P_{adj}, *P* value for association after adjusting for covariates of sex, age, HTN, CAD and DM by multiple logistic regression analysis using SPSS v17.0;
OR, odds ratio;
95% CI, 95% confidential interval.

Table 4. Estimation of AF heritability explained by SNPs showing significant association in the Chinese Han population.

Locus	AF heritability explained
rs13216675 (near the *GJA1*)	1.8%
rs6584555 (*NEURL*)	3.7%
rs6490029 (*CUX2*)	2.6%
rs2200733 (near *PITX2*)	1.8%
rs2106261 (*ZFHX3*)	1.7%
rs3807989 (*CAV1*)	2.9%
Total	**14.5%**

Acknowledgments

This study was supported by the China National Natural Science Foundation grants (31430047, 81630002, 81600263 and 91439129), 2016 Top-Notch Innovative Talent Development Project from the Bureau of Human Resources and Social Security of Wuhan City, the Chinese National Basic Research Program (973 Project 2013CB531101), NIH/NHLBI grants R01 HL121358 and R01 HL126729, Hubei Province Natural Science Programs (2016CFB224 and 2014CFA074), and the Hubei Province's Outstanding Medical Academic Leader Program.

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