ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2595–2598
doi:10.1093/eurheartj/ehx289

EDITORIAL

Genetic heterogeneity of atrial fibrillation susceptibility loci across racial or ethnic groups

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Online publish-ahead-of-print 14 June 2017

This editorial refers to 'Korean atrial fibrillation network genome-wide association study for early-onset atrial fibrillation identifies novel susceptibility loci'†, by J.-Y. Lee *et al.*, on page 2586.

Atrial fibrillation (AF) is a major global health problem due to its serious associated complications and financial burden on patients, healthcare systems, and society. Approximately 33 million people worldwide today carry the diagnosis of AF.[1] Ageing of the population especially in Western countries may in part be responsible for the increasing incidence and prevalence of AF, but the identification of newer risk factors such as race, obstructive sleep apnoea, obesity, and metabolic syndrome may also contribute to this global epidemic. However, some patients develop AF in the absence of established or novel risk factors, suggesting a genetic susceptibility to the condition in the general population. Data from the Framingham study showed that a family history of AF may increase the risk of developing AF in an individual of European descent by up to three-fold.[2]

The pathophysiology of AF is complex, and much of our current understanding of the genetic basis of AF is derived from studies examining mostly white patients of European descent. However, marked discrepancies in the prevalence of AF and influence of known risk factors between white and non-white populations have become increasingly recognized. It is now established that African Americans are less susceptible to AF than whites of European descent despite a greater burden of traditional risk factors. In a large Japanese community cohort, the prevalence of AF was shown to be only two-thirds that of similarly aged patients in the USA.[3] While similar findings have also been confirmed in Chinese cohorts, it remains unknown whether the AF paradox also applies to patients of Hispanic/Latino descent. However, ongoing studies at our centre and others will determine if Hispanic/Latino subjects are also less prone to develop AF as compared with their white counterparts.

Few studies have examined the role of common genetic variants in mediating the AF paradox in non-white populations. Marcus *et al.*[4] were the first to show that the proportion of European ancestry in African Americans was associated with increased susceptibility to AF. The same group also went on to conduct admixture mapping, a technique particularly suited for populations with mixed ancestry such as African Americans, with the goal of identifying novel genetic loci. Roberts *et al.*[5] identified a previously known AF risk allele on chromosome 10q22 that partially mediated a higher risk for AF in European Americans as compared with African Americans. Furthermore, they also showed that this single nucleotide polymorphism (SNP) was not only AF protective and occurred more commonly in blacks but that it also accounted for 11–32% of the reduced risk for AF in this ethnic group. Failure to identify any AF-associated SNPs with admixture mapping at the pre-specified genome-wide significance level may relate to inadequate power. However, it should be appreciated that the meta-analysis involved >5000 African Americans and constituted the largest black cohort that has undergone genome-wide association analysis. Nonetheless, this finding highlights a major challenge when performing genome-wide association studies (GWASs) across racial/ethnic groups, i.e. the need to recruit tens of thousands of individuals with and without AF in order to meet pre-specified statistical significance.

Prior GWASs conducted in mostly white patients of European ancestry have identified 14 AF susceptibility loci (*Table 1*).[6,7] However similar results have not been as well replicated in subsequent GWAS and case–control association studies conducted in Asian populations.[8] In this issue of the journal, Lee *et al.*[9] report the results of the latest GWAS from the Korean AF Network. The discovery cohort consisted of 672 Korean patients with early-onset AF (age <60 years[6]) who had undergone radiofrequency catheter ablation for AF and a control group of 3700 patients without AF from a large community cohort. The replication cohort included 200 patients with AF and 1812 controls. Patients with early-onset AF in the discovery cohort were predominantly male (80%) and most were categorized as having paroxysmal AF (72%). Risk factors were less favourable for both case groups, with the exception of lower prevalence of diabetes in the control group of the replication cohort.

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† doi:10.1093/eurheartj/ehx213.

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Table 1 Top common genetic variants associated with atrial fibrillation in African American, Chinese, European, Japanese, and Korean cohorts identified by genome-wide analysis

SNP	Locus	Closest gene	MAF (%)	RR (95% CI)	*P*-value
African American[13]					
rs998259	14q22	*GCH1*	96.0	NA	3.59×10^{-6}
rs4758417	11p15	*HPX*	98.0	NA	1.44×10^{-5}
rs5436	17p13	*SLC2A4*	91.0	NA	3.16×10^{-5}
rs93267	8p12	*NRG1*	92.0	NA	1.98×10^{-5}
rs4246336	15p26	*PCSK6*	43.0	NA	3.8×10^{-4}
rs4611994	4q25	*PITX2*	21.0	1.40 (1.16–1.69)	5.4×10^{-4}
Chinese[14, 15]					
rs2200733	4q25	*PITX2*	64.6	1.81 (1.21–3.20)	1.3×10^{-10}
rs3807989	7q31	*CAV1*	24.5	1.42 (1.20–1.68)	4.77×10^{-5}
rs2106262	16q22	*ZFHX3*	39.0	1.32 (1.15–1.51)	1.97×10^{-4}
European[6 7]					
rs2200733	4q25	*PITX2*	25.8	1.71 (1.54–2.21)	6.1×10^{-41}
rs12415501	10q24	*NEURL*	16.0	1.18 (1.13–1.23)	6.5×10^{-16}
rs7193343	16q22	*ZFHX3*	17.6	1.25 (1.17–1.3)	1.8×10^{-15}
rs13376333	1q21	*KCNN3*	29.5	1.56 (1.38–1.77)	6.3×10^{-12}
rs3903239	1q24	*PRRX1*	44.7	1.14 (1.10–1.18)	9.1×10^{-11}
rs10507248	12q24	*TBX5*	73.0	1.12 (1.08–1.16)	5.7×10^{-11}
s3807989	7q31	*CAV1*	40.4	0.88 (0.84–0.91)	9.6×10^{-11}
rs1152591	14q23	*SYNE2*	47.6	1.13 (1.09–1.18)	6.2×10^{-10}
rs13216675	6q22	*GJA1*	68.0	1.10 (1.06–1.14)	2.2×10^{-9}
rs6490029	12q24	*CUX2*	64.0	1.12 (1.08–1.16)	3.9×10^{-9}
rs10821415	9q22	*C9orf3*	42.4	1.13 (1.08–1.18)	7.9×10^{-9}
rs4642101	3p25	*CAND2*	65.0	1.10 (1.06–1.14)	9.8×10^{-9}
rs7164883	15q24	*HCN4*	16.0	1.16 (1.10–1.22)	1.3×10^{-8}
rs10824026	10q22	*SYNPO2L*	15.8	0.85 (0.81–0.9)	1.7×10^{-8}
Japanese[10]					
rs2220427	4q25	*PITX2*	45.0	1.71 (1.63–1.78)	1.65×10^{-134}
rs21061	16q22	*ZFHX3*	31.0	1.33 (1.27–1.39)	9.63×10^{-36}
rs6584555	10q24	*NEURL*	12.0	1.32 (1.26–1.39)	2.0×10^{-25}
rs7698692	4q34	*HAND2*	54.2	1.17 (1.13–1.21)	1.21×10^{-21}
rs17461925	1q32	*PPFIA4*	82.0	1.20 (1.15–1.25)	8.69×10^{-18}
rs2047036	10q24	*SH3PXD2A*	28.4	1.16 (1.12–1.20)	4.04×10^{-16}
rs2540953	2p14	*SLC1A4-CEP68*	67.4	1.15 (1.11–1.20)	2.06×10^{-15}
rs12044963	1p13	*KCND3*	52.0	1.14 (1.10–1.17)	2.52×10^{-15}
rs2296610	10p12	*NEBL*	14.5	1.20 (1.15–1.26)	1.51×10^{-14}
rs1049334	7q31	*CAV1*	71.0	1.20 (1.15–1.26)	1.83×10^{-14}
rs6490029	12q24	*TBX5/CUX2*	65.0	1.12 (1.08–1.16)	3.9×10^{-9}
rs639652	1q24	*PRRX1*	54.0	1.13 (1.08–1.18)	4.43×10^{-9}
rs13219206	6q22	*GJA1-HSF2*	72.0	1.14 (1.09–1.20)	3.52×10^{-8}
Korean[9]					
rs6817105	4q25	*PITX2*	52.5	2.43 (2.12–2.78)	6.01×10^{-38}
rs2106261	16q22	*ZFHX3*	34.8	2.08 (1.83–2.36)	3.32×10^{-30}
rs4615152	4q34	*HAND2*	42.0	1.51 (1.35–1.68)	1.43×10^{-12}
rs11579055	1q32	*PPFIA4*	69.0	1.48 91.30–1.68)	2.29×10^{-9}
rs3903239	1q24	*PRRX1*	54.3	1.14 (1.24–1.60)	1.25×10^{-7}
rs6584555	10q24	*NEURL*	12.6	1.58 (1.33–1.88)	2.77×10^{-7}
rs883079	12q24	*TBX5*	43.2	1.19 (1.05–1.35)	0.006

CI, confidence interval; MAF, minor allele frequency; NA, not available; RR, relative risk; SNP, single nucleotide polymorphism.

Because of differences in baseline characteristics between the groups, analysis was performed using a propensity score matching model.

The authors found that 5 of the 14 susceptibility loci previously identified by GWAS of patients of European ancestry were reproducibly associated with AF in this cohort of Korean patients with early-onset AF who underwent catheter ablation. The five shared genetic loci were (according to decreasing magnitude of AF association): 4q25/*PITX2* rs17042171, 16q22/*ZFHX3* rs2106261, 10q24/*NEURL* rs6584554, 1q24/*PRRX1* rs3903239, and 12q24/*TBX5* rs883079. Another significant finding of the study was the discovery of two novel risk loci at 1q32.1 (*PPFIA4*) and 4q34 (*HAND2*) specifically associated with early-onset AF in the Korean cohort.

The findings of the present study raise and highlight some of the challenges when conducting GWASs in diverse racial/ethnic groups. First, one potential explanation for why only 5 of the 14 AF risk loci identified in Europeans were replicated in the Korean cohort may relate to inadequate power. Low *et al.*[10] recently identified common AF risk alleles at chromosome 1q32 and 4q34 loci but also demonstrated additional novel susceptibility loci near the genes for *KCND3*, *SLC1A4-CEP68*, *NEBL*, and *SH3PXD2A* in a GWAS of a large Japanese cohort. While the GWAS in the Korean cohort was performed in a highly selected group of patients with early-onset AF who underwent ablation for symptom control, Low *et al.*[10] examined a much larger cohort (>8000 AF cases, >28 000 controls) and it can only be postulated whether additional power would have replicated the other four AF risk loci in a similarly sized Korean cohort. Secondly, compared with European cohorts, the minor allele frequency (MAF) was higher for common variants at *PITX2*, rs6817105 (52.5% vs. 13.1%) and *ZFHX3*, rs2106261 (34.8% vs. 17.6%), but lower for *KCNN3*, rs6666258 (1.8% vs. 29.9%) and *HCN4*, rs7164883 (8.4% vs. 16%) in the Korean cohort. So, differing MAFs across racial/ethnic groups may be another explanation for why only five AF risk loci were replicated in the Korean cohort (*Table 1*). Thirdly, it is possible that AF susceptibility loci are truly genetically heterogeneous across racial/ethnic groups, and this hypothesis is supported not only by the study of Lee *et al.*[9] but also by the recent AF GWAS report in a Japanese cohort where an additional five novel AF risk loci were identified. Nonetheless, it should be emphasized that common genetic variants at the chromosome 4q25 and 16q22 loci have consistently been associated with AF and replicated across multiple diverse racial and ethnic groups.

The findings of the study of Lee *et al.*[9] are novel in that the identification of two novel AF risk SNPs in a Korean cohort with early-onset AF may help elucidate reasons for ethnic variation in AF patterns between patients of European and Asian descent and affect future treatment approaches. The investigators performed expression quantitative trait locus (eQTL) mapping of the two AF risk loci. The top SNP rs11579055 at chromosome 1q32 was associated with increased expression of PPFIA4 in whole blood. *PPFIA4* encodes liprin-α4, which regulates cell–matrix interaction and synapse maturation.[11] Along with the discovery of a susceptibility locus at 10q24 (*SH3PXD2A*),[10] the findings seem to suggest that axon guidance and focal cell adhesion may play a unique role in the pathogenesis of AF in patients of Asian descent. The other susceptibility locus on chromosome 4q34 is near the *HAND2* gene which expresses a protein believed to be involved in regenerative cardiomyocyte proliferation and is also known to play a role in cardiac morphogenesis.[12] However, to confirm causality between a genetic variant and AF nowadays mandates functional characterization in a heterologous expression system and/or expression in a mammalian model. Functional characterization of ion channel genetic variants using heterologous expression may be insufficient as it may miss the impact of key associated proteins. Hence, expression of a mutated ion channel or protein should entail expression in a mammalian model system.

In summary, Lee *et al.*[9] identified and replicated the two most common AF susceptibility loci identified in patients of European descent in a Korean cohort with early-onset AF and uncovered two additional novel AF risk SNPs. The present study's findings along with a recent GWAS in a Japanese cohort strongly support the concept of genetic heterogeneity in AF susceptibility loci across racial/ethnic groups. Such knowledge may not only elucidate the underlying molecular mechanisms of AF in diverse racial/ethnic groups but also permit a more 'personalized' mechanism-based approach to the management of this common and morbid condition.

Funding

This work was in part supported by NIH R01 HL092217 and R01 HL124935.

Conflict of interest: none declared.

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