70. Genetic Predisposition According to the Age at the Onset of Atrial Fibrillation

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Body

Background: Although atrial fibrillation (AF) is a heritable disease, multiple comorbid factors, including aging, contribute to its development. We investigated the association between a weighted genetic risk score (wGRS) for AF and the age at onset.

Methods: We included 1,968 patients with AF (Yonsei AF Ablation cohort) and 5,486 controls from the Korean Genome Epidemiology Study (KoGES). After 1:1 matching, 1,416 patients and 1,416 controls were included in the analyses. The age of AF onset was determined by the first electrocardiogram (ECG) documentation.

Results: We selected nine previously reported AF-associated single-nucleotide polymorphisms (SNPs). Among nine proven AF-associated SNPs, 4 genes (PRRX1, PPFIA4, PITX2, and ZFHX3) were independently associated with the age at the onset of AF ($p<0.05$), but no associated genes were found in the controls. In the quartile and multivariate analyses, the lower quartile age at the onset of AF had a higher wGRS ($p<0.001$), and a younger age at the onset of AF was independently associated with the wGRS (-0.29 [-0.57--0.01], $p=0.045$), but that association was not observed in the control cohort. Contrarily, the higher quartile of the wGRS group had a younger age of AF onset ($p<0.001$), and the wGRS was independently associated with the age at onset of AF (-0.02 [-0.03--0.01], $p=0.002$). In the subgroup analyses, these age-wGRS associations were significant in males ($p<0.001$) and in those without heart failure ($p<0.001$) or strokes ($p<0.001$).

Conclusion: AF-associated genetic loci significantly contributed to the age at the onset of AF, as determined by the first ECG.

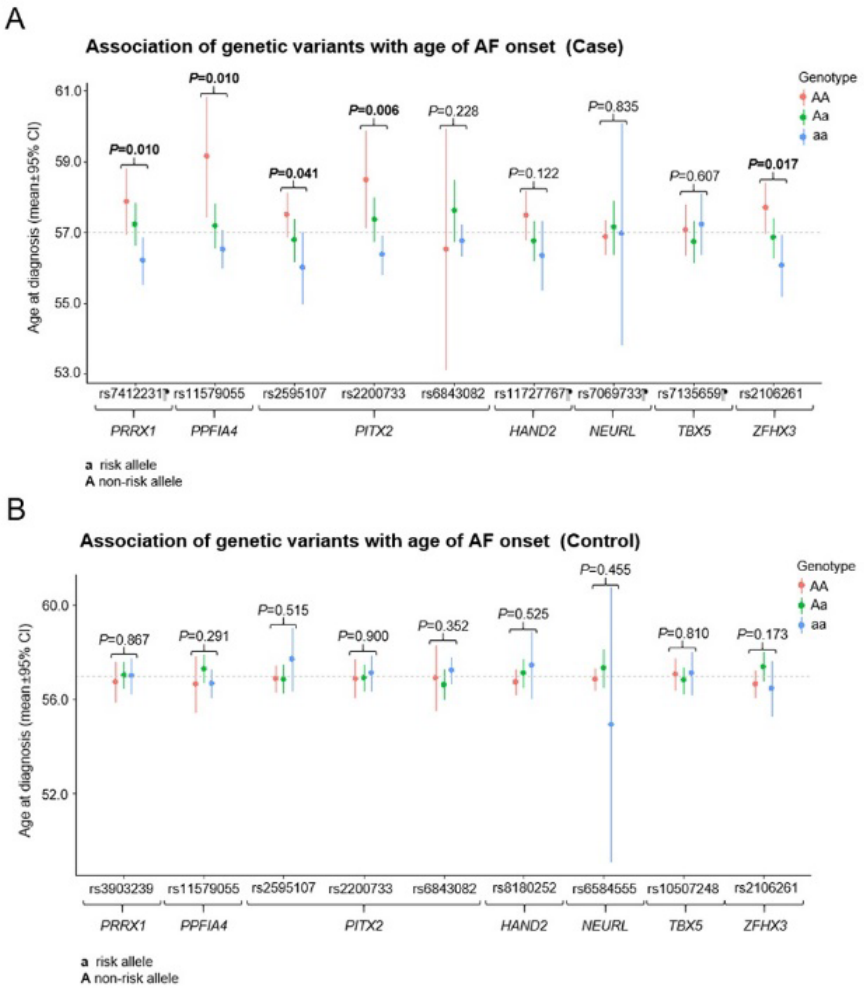
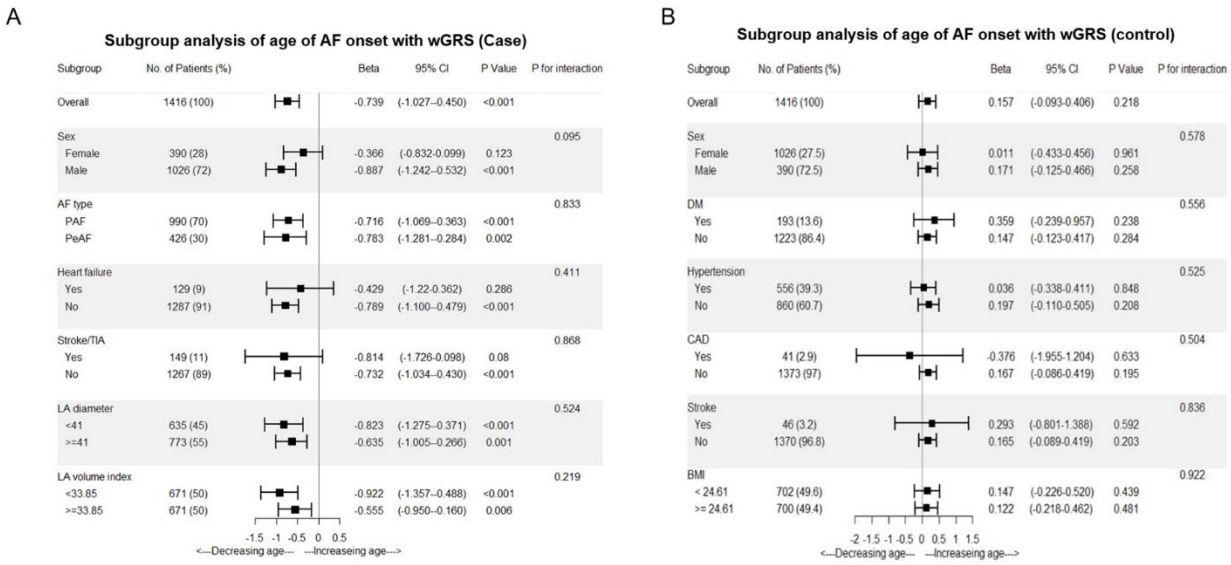

A
Association of genetic variants with age of AF onset (Case)
Genotype
AA
Aa
aa
Age at diagnosis (mean±95% CI)
61.0
59.0
57.0
55.0
53.0
P=0.010
P=0.010
P=0.041
P=0.006
P=0.228
P=0.122
P=0.835
P=0.607
P=0.017
rs7412231
rs11579055
rs2595107
rs2200733
rs6843082
rs11727767
rs7069733
rs7135659
rs2106261
PRRX1
PPFIA4
PITX2
HAND2
NEURL
TBX5
ZFHX3
a risk allele
A non-risk allele
B
Association of genetic variants with age of AF onset (Control)
Genotype
AA
Aa
aa
Age at diagnosis (mean±95% CI)
60.0
56.0
52.0
P=0.867
P=0.291
P=0.515
P=0.900
P=0.352
P=0.525
P=0.455
P=0.810
P=0.173
rs3903239
rs11579055
rs2595107
rs2200733
rs6843082
rs8180252
rs6584555
rs10507248
rs2106261
PRRX1
PPFIA4
PITX2
HAND2
NEURL
TBX5
ZFHX3
a risk allele
A non-risk allele

Figure 1



Clinical Implications: Although atrial fibrillation (AF) is a heritable disease, a genetic predisposition according to the age of onset has not been clearly demonstrated. We investigated the association between the age of onset of AF and AF risk using AF genetic variants. Among 9 proven AF-associated SNPs, 4 genes (PRRX1, PPFIA4, PITX2, and ZFHX3) and the wGRS for 4 genes were independently associated with the age of onset of AF, but none of them were associated with the age of the non-AF control. The AF risk detected by AF associated genes is a clinically useful predictor of the age of onset of AF with a mechanistic relationship determined by the first electrocardiogram (ECG)