Predicting atrial fibrillation using a combination of genetic risk score and clinical risk factors

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BACKGROUND Atrial fibrillation (AF) has a genetic basis, and environmental factors can modify its actual pathogenesis.

OBJECTIVE The purpose of this study was to construct a combined risk assessment method including both genetic and clinical factors in the Japanese population.

METHODS We screened a cohort of 540 AF patients and 520 non-AF controls for single nucleotide polymorphisms (SNPs) previously associated with AF by genome-wide association studies. The most strongly associated SNPs after propensity score analysis were then used to calculate a weighted genetic risk score (WGRS). We also enrolled 1018 non-AF Japanese subjects as a validation cohort and monitored AF emergence over several years. Finally, we constructed a logistic model for AF prediction combining WGRS and clinical risk factors.

RESULTS We identified 5 SNPs (in *PRRX1*, *ZFHX3*, *PITX2*, *HAND2*, and *NEURL1*) associated with AF after Bonferroni correction. There was a 4.92-fold difference in AF risk between the highest and lowest WGRS calculated using these 5 SNPs ($P = 2.32 \times 10^{-10}$). Receiver operating characteristic analysis of WGRS yielded an area under the curve (AUC) of 0.73 for the screening cohort and 0.72 for the validation cohort. The predictive logistic model constructed using a combination of WGRS and AF clinical risk factors (age, body mass index, sex, and hypertension) demonstrated better discrimination of AF than WGRS alone (AUC = 0.84; sensitivity 75.4%; specificity 80.2%).

CONCLUSION This novel predictive model of combined AF-associated SNPs and known clinical risk factors can accurately stratify AF risk in the Japanese population.

KEYWORDS Atrial fibrillation; Clinical risk factors; Genetic risk score; Risk stratification; Single nucleotide polymorphisms

(Heart Rhythm 2020;17:699–705)

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and a major contributor to stroke and cardiovascular mortality.[1] The incidence of cerebral infarction from nonvalvular AF is approximately 5% per year, approximately 2–7 times higher than in the matched population without AF.[2,3] Early AF detection and therapeutic intervention are imperative because stroke prevention in high-risk AF patients is now possible with anticoagulant therapy.

Several studies have demonstrated a genetic basis for AF and modulation of AF pathogenesis by environmental factors.[4,5] Genome-wide association studies (GWASs) have identified several common single nucleotide polymorphisms (SNPs) that influence AF risk.[6,7] The most recent largest AF meta-analysis revealed 97 AF-associated loci in a mainly European population.[8]

Even in the Asian population including Japanese, 26-AF associated SNPs were demonstrated in previous GWASs.[9–11] In addition to genetic factors, multiple clinical factors have been implicated in AF risk, such as hypertension, diabetes, aging, male sex, obesity, smoking, ischemic heart disease, valvular heart disease, and congestive heart failure.[12–14]

Stratification of AF risk is required for early AF detection and intervention to reduce the mortality caused by cerebral

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1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2020.01.006

infarction or heart failure and the associated medical costs. We hypothesized that combining genetic and clinical risk factors can stratify AF risk more accurately than either alone. In this study, we constructed a novel risk model that includes both genetic and clinical risk factors to predict AF in the Japanese population.

Methods

Study participants

We retrospectively enrolled 565 Japanese patients with AF treated at Hiroshima University Hospital between November 2009 and April 2012. We excluded those with severe valvular disease (n = 1), congenital heart disease (n = 2), ischemic heart disease (n = 10), hypertrophic cardiomyopathy (n = 11), and dilated cardiomyopathy (n = 1). The remaining 540 Japanese AF patients were included as screening subjects. We also enrolled 520 Japanese non-AF controls from Hiroshima University as screening non-AF controls. This group excluded candidates with cardiac disease, hyperthyroidism, severe liver dysfunction, or kidney dysfunction. We also enrolled 1018 Japanese outpatients deemed non-AF by electrocardiography or Holter monitoring at Hiroshima University Hospital between May 2012 and August 2016 as a replication cohort. This group was prospectively monitored for AF emergence. In brief, electrocardiography and physical examination were conducted at each outpatient appointment. Participants were diagnosed with AF if arrhythmia was recorded by 12-lead electrocardiogram, Holter monitor, or portable electrocardiogram by either our hospital staff or external clinicians. Other relevant clinical parameters (age, sex, body mass index [BMI], hypertension, and diabetes) were obtained from medical records. According to the results of the previous Japanese large-scale cohort study, we used these parameters as conventional clinical risk factors.[14]

Hypertension was defined as a systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or usage of antihypertensive medication. Diabetes was defined as glycated hemoglobin (HbA_{1c}) $\geq$48 mmol/mol (6.5% DCCT [Diabetes Control and Complications Trial]) or usage of antidiabetic medications. BMI was defined as body weight in kilograms divided by the square of height measured in meters. The study was approved by the Institutional Ethics Committee of the Graduate School of Biomedical Science at Hiroshima University and conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to the standard protocol. The following 26 SNPs reported in a previous GWAS[6–10,15] were genotyped using the TaqMan or Invader assay: *KCNN3* (rs6666258), *PRRX1* (rs3903239), *IL6R* (rs1126561), *CAV1* (rs3807989), *C9orf3* (rs1082141), *HCN4* (rs7164883), *ZFHX3* (rs2106261), *PTIX2* (rs6817105), *SYNE2* (rs1152591), *SYNPO2L* (rs10824026), *MYOZ1* (rs3740293), *HSPB7* (rs10927875), *WINTA8A* (rs2040862), *NEBL* (rs229661), *SLC1A4–CEP68* (rs2540953), *PPFIA4* (rs17461925), *SH3PXD2A* (rs2047036), *KCND3* (rs12044963), *HAND2* (rs7698692), *CAND2* (rs7626624), *GJA1–HSF2* (rs13219206), *NEURL1* (rs60572254), *CUX2* (rs4766566), *HBEGF* (rs13385), *KCNJ5* (rs75190942), and *titin* (rs12614435).

Calculating weight genetic risk score

The weighted genetic risk score (WGRS) was calculated from the AF-associated SNPs identified in this study using logistical regression analysis. The risk estimate for the minor allele of each SNP was obtained from the odds ratio. The natural log-transformed risk estimate for the minor allele was multiplied by the number of minor alleles (0, 1, 2) for each SNP, and these products were summed to yield the individual WGRS for each subject.

Statistical analysis

Normally distributed continuous variables are reported as mean $\pm$ SD. Group means were compared by the Welch t-test or 1-way analysis of variance with Tukey-Kramer *post hoc* tests for pair-wise comparisons. Propensity score methods were used for adjustment of confounding factors in the screening cohort. Logistical regression analysis was used to identify predictive factors for AF. To test the additive genetic effect for the minor allele, common alleles were coded as 0 (reference), 1 (heterozygous for the minor allele), or 2 (homozygous for the minor allele). Deviation from Hardy–Weinberg equilibrium was tested in the AF and non-AF controls using the χ^2 test. $P < .05$ was considered significant. The Bonferroni-corrected P value threshold for SNP discovery was $P < .0019$ (0.05/26). The odds ratio and 95% confidence interval (CI) were calculated for the reference allele or the genotype. To test the genetic relationships between cases and controls, we used the χ^2 test and the Cochran–Armitage trend test. The log-rank test was applied to compare the cumulative incidence of AF between groups. All statistical analyses were conducted using R3.3.1 and the JMP statistical package version 13 (SAS Institute, Cary, NC).

Results

Baseline patient characteristics and genotype distribution in the screening cohort

Baseline characteristics of the AF and the non-AF controls in the screening cohort are presented in Table 1. Compared to the non-AF group, the AF patients were older (59.1 $\pm$ 10.1 years vs 49.9 $\pm$ 14.7 years; $P = 5.01 \times 10^{-30}$), more likely to be male (72.5% vs 48.0%; $P = 2.27 \times 10^{-16}$), more likely to have higher BMI (24.3 $\pm$ 3.4 vs 22.4 $\pm$ 3.4; $P = 7.96 \times 10^{-20}$), more likely to have hypertension (56.4% vs 18.2%; $P = 3.07 \times 10^{-35}$), and more likely to have diabetes (16.7% vs 6.7%; $P = 2.73 \times 10^{-7}$). We performed propensity score matching to accommodate these differences in

Table 1 Baseline characteristics of AF patients and non-AF control subjects before and after propensity score matching in the screening cohort

	Original sample				Matched sample			
	AF	Non-AF control			AF	Non-AF control		
Variable	(N = 540)	(N = 520)	SD	*P* value	(N = 287)	(N = 287)	SD	*P* value
Age (y)	59.1 ± 10.1	49.9 ± 14.7	0.97	5.01×10^{-30}	56.8 ± 10.8	57.0 ± 12.9	0.02	.84
Male	392 (72.5)	252 (48.0)	0.38	2.27×10^{-16}	187 (65.2)	185 (64.6)	0.01	.86
BMI	24.3 ± 3.4	22.4 ± 3.4	0.69	7.96×10^{-20}	23.5 ± 3.1	23.6 ± 3.5	0.04	.54
Hypertension	304 (56.4)	87 (18.2)	1.12	3.07×10^{-35}	102 (35.5)	94 (32.8)	0.06	.48
Diabetes	90 (16.7)	35 (6.7)	0.29	2.73×10^{-7}	30 (10.5)	26 (9.1)	0.03	.57

Values are given as mean ± standard deviation or n (%) unless otherwise indicated.
AF = atrial fibrillation; BMI = body mass index; SD = standardized difference, where SD (of means) <0.25 indicates good balance between groups.

baseline characteristics (Table 1). The standardized difference of the matched samples demonstrated that AF patients and controls were well balanced after matching.

Association of GWAS reported SNPs and AF in the screening cohort

After propensity score matching, 5 SNPs were associated with AF (Table 2): rs3903239 (*PRRX1*), rs2106261 (*ZFHX3*), rs6817105 (*PITX2*), rs7698692 (*HAND2*), and rs6057225 (*NEURL1*).

We confirmed that the same 5 SNPs were significantly associated with AF by another propensity method (stratification and covariate adjustment on the propensity score) and logistic regression analysis in the replication cohort (Supplemental Tables 1 and 2).

WGRS for predicting AF in the screening cohort

We compared the WGRS calculated using all 26 SNPs (26-WGRS) with the WGRS using only the significant 5 SNPs (5-WGRS). The AUC of the receiver operating characteristic (ROC) analysis using 26-WGRS in the screening cohort was lower than that of 5-WGRS (0.70 vs 0.73; $P = 1.09 \times 10^{-3}$) (Supplemental Figure 1). Therefore, we decided to adopt the WGRS using the significant 5 SNPs in this study.

The mean WGRS value was higher in AF patients than non-AF controls (3.62 ± 1.31 vs 2.84 ± 1.34; $P = 6.89 \times 10^{-12}$) (Figure 1). Individual WGRSs were stratified into quartile groups (groups 1–4) for comparison of AF and various clinical factors. The ratio of AF to non-AF controls increased with WGRS quartile, and there was a 4.92-fold difference in odds ratio between the highest and lowest WGRS (Figure 2). The mean age of AF onset (years) also decreased progressively with higher WGRS quartile (group 1: 63.2 ± 9.9 years; group 2: 61.5 ± 11.2 years; group 3: 61.0 ± 10.8 years; group 4: 57.8 ± 10.2 years) (Supplemental Figure 2), and the difference was statistically significant between groups 1 and 4.

ROC analysis of WGRS for AF prediction in the screening cohort yielded AUC of 0.73 ($P = 1.85 \times 10^{-13}$; sensitivity 65.4%; specificity 69.6%) (Supplemental Figure 3). The AUC of each SNP in the screening cohort was as follows; rs3903239 (*PRRX1*), 0.57; rs2106261 (*ZFHX3*), 0.61; rs6817105 (*PITX2*), 0.70; rs7698692 (*HAND2*), 0.55; and rs6057225 (*NEURL1*), 0.61). Thus, WGRS predicted AF occurrence more accurately than any single SNP.

Baseline patient characteristics and WGRS in the replication cohort

Baseline characteristics and mean WGRS of the replication cohort are listed in Table 3. During the follow-up period of 4.7 years, AF was diagnosed in 273 subjects (26.8%). On average, compared to non-AF patients, those with AF were older (age 52.7 ± 11.3 years vs 44.6 ± 14.2 years; $P = 3.46 \times 10^{-24}$), were more likely to be male (75.1% vs 55.3%; $P = 4.52 \times 10^{-13}$), were heavier (BMI: 24.1 ± 3.4 vs 22.4 ± 3.2; $P = 6.13 \times 10^{-17}$), and had greater incidences of hypertension (44.3% vs 20.6%; $P = 2.78 \times 10^{-12}$) and diabetes (12.8% vs 5.2%; $P = 2.08 \times 10^{-7}$), consistent with the AF group in the screening cohort. Mean WGRS was also significantly higher in the AF group than the non-AF group in the replication cohort (3.79 ± 1.18 vs 2.89 ± 1.20; $P = 3.58 \times 10^{-13}$).

Cumulative incidence of AF according to WGRS in the replication cohort

The utility of WGRS for AF prediction was validated by ROC analysis. AUC was 0.72, consistent with the screening cohort, and a cutoff WGRS of 4.01 yielded 65.4% sensitivity and 69.6% specificity. The cumulative incidences of AF for the 2 groups divided by this WGRS cutoff are shown in Figure 3. The high-risk group (WGRS ≥4.01) was significantly more likely to develop AF than the low-risk group (WGRS <4.01) (40.9% vs 16.1%; log-rank $P = 2.57 \times 10^{-18}$).

Multivariate analysis of AF-associated clinical factors in the replication cohort

Multivariate regression analysis including significant factors from univariate analysis was performed (Table 4). For continuous variables (age and BMI), an optimal cutoff value was calculated by ROC curve analysis in the replication cohort and used. We found significant independent associations of AF with age >50 years (hazard ratio [HR] 3.42; 95% CI 2.35–4.96; $P = 9.95 \times 10^{-11}$), male sex (HR 2.38; 95% CI 1.68–3.42; $P = 1.86 \times 10^{-4}$), BMI >25kg/m^2 (HR 2.53;

Table 2 Association of the 26 SNPs with AF after propensity score matching in the screening cohort

SNP	rs ID	Allele 1/2	AF (N = 287)			Control (N = 287)			OR	95% CI	*P* value	HW test
			11	12	22	11	12	22				
KCNN3	rs6666258	C vs G	0	11	276	0	16	271	1.378	0.709–2.821	.49	0.64
PRRX1	rs3903239	A vs G	29	139	119	59	143	85	1.687	1.236–2.242	4.24×10^{-5}	0.29
IL6R	rs1126561	A vs G	75	139	73	74	149	64	1.118	0.846–1.412	.42	0.78
CAV1	rs3807989	A vs G	26	134	127	25	125	137	1.089	0.768–1.282	.97	0.84
C9orf3	rs10821415	A vs C	19	121	147	15	98	176	1.255	1.042–1.873	.02	0.34
HCN4	rs7164883	A vs G	221	73	4	227	57	3	1.086	0.587–1.746	.76	0.93
ZFHX3	rs2106261	C vs T	99	143	46	146	109	32	1.928	1.291–2.574	3.87×10^{-6}	0.76
PITX2	rs6817105	C vs T	130	121	36	53	162	73	2.792	1.962–3.534	4.84×10^{-13}	0.37
SYNE2	rs1152591	A vs G	38	144	106	29	145	113	1.235	0.868–1.632	.12	0.36
SYNPO2L	rs10824026	A vs G	93	153	41	112	122	53	1.028	0.687–1.432	.63	0.24
MYOZ1	rs3740293	A vs C	168	110	10	176	103	8	1.011	0.818–1.392	.87	0.23
HSPB7	rs10927875	C vs T	285	2	0	286	1	0	1.892	0.285–2.742	.63	0.97
WINT8A	rs2040862	C vs T	287	0	0	287	1	0	—	—	1	0.97
NEBL	rs2296610	G vs T	223	63	1	227	59	2	1.053	0.823–1.476	.76	0.12
SLC1A4-CEP68	rs2540953	G vs A	146	124	18	135	121	27	1.132	0.925–1.512	.29	0.98
PPFIA4	rs17461925	A vs G	213	72	2	201	79	7	1.113	0.843–1.571	.27	0.91
SH3PXD2A	rs2047036	C vs T	21	134	133	16	129	143	1.289	0.854–1.692	.19	0.26
KCND3	rs12044963	G vs T	75	139	73	81	136	70	1.015	0.734–1.212	.89	0.08
HAND2	rs7698692	A vs G	109	120	58	54	157	76	1.592	1.172–1.981	2.64×10^{-4}	0.72
CAND2	rs7626624	C vs A	0	284	3	0	285	2	1.001	0.946–1.143	.92	2.68×10^{-43}
GJA1–HSF2	rs13219206	C vs T	161	95	21	167	102	8	1.142	0.741–1.284	.89	0.31
NEURL1	rs6057225	C vs T	207	72	8	242	42	3	1.965	1.182–2.726	3.76×10^{-5}	0.18
CUX2	rs4766566	C vs T	34	120	133	24	135	128	1.121	0.768–1.370	.63	0.42
HBEGF	rs13385	G vs A	133	123	31	134	121	32	1.075	0.765–1.391	.18	0.09
KCN5	rs75190942	C vs A	255	31	1	259	28	0	1.112	0.715–1.929	.32	0.31
Titin	rs12614435	A vs G	79	145	63	82	140	65	1.018	0.898–1.275	.87	0.27

AF = atrial fibrillation; CI = confidence interval; HW test = Hardy-Weinberg equilibrium test; OR = odds ratio; SNP = single nucleotide polymorphism.

95% CI 1.77–3.58; $P = 2.56 \times 10^{-7}$), hypertension (HR 1.63; 95% CI 1.14–2.31; $P = 6.52 \times 10^{-3}$), and WGRS >4.01 (HR 3.27; 95% CI 2.37–4.52; $P = 6.72 \times 10^{-13}$).

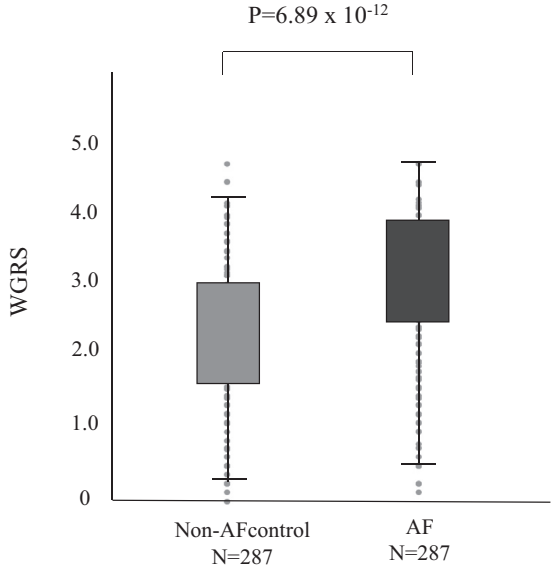


Figure 1 Mean weighted genetic risk score (WGRS) for patients with atrial fibrillation (AF) and non-AF controls within the screening cohort. Mean WGRS was significantly higher in patients with AF than in non-AF controls (3.62 ± 1.31 vs 2.84 ± 1.34; $P = 6.89 \times 10^{-12}$).

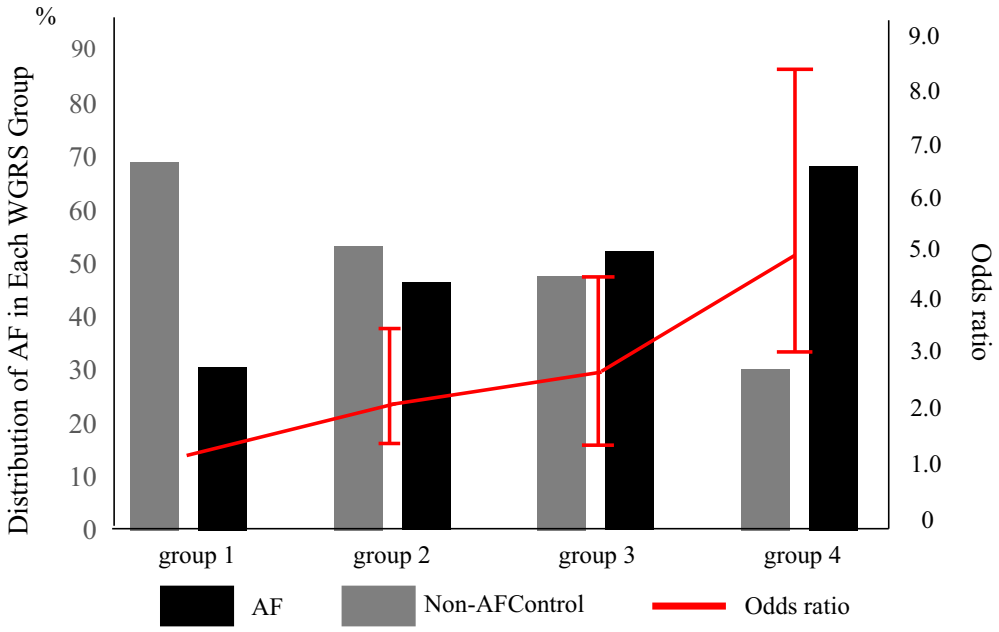
The weighted clinical risk score (CRS) was calculated by combining the clinical risk factors using these HRs. Individual CRSs were divided into quartile groups (groups 1–4). The ratio of AF to non-AF controls increased with CRS quartile, and there was an 8.51-fold difference in odds ratio between the highest and lowest CRS (Supplemental Figure 4).

Risk prediction models for AF in the replication cohort

The AUC of CRS was slightly higher than that of WGRS (0.79 [70.9% sensitivity, 74.3% specificity] vs 0.72 [65.4% sensitivity, 69.6% specificity]; $P = 1.03 \times 10^{-4}$). Thus, clinical factors also strongly influence AF risk. Therefore, we constructed a predictive logistical model combining WGRS and the CRS. This model showed significantly better discrimination of AF (AUC 0.84; sensitivity 75.4%; specificity 80.2%) than either WGRS or CRS alone (Figure 4).

Discussion

Almost half of AF patients are asymptomatic, and these patients die of associated cardiovascular events at a rate 3 times higher than symptomatic AF patients.[16] Thus, early AF detection is critical for reducing mortality. Various new technologies, such as wearable electrocardiographic patches, Apple watch/smartphones, and irregular beats-detecting blood pressure machines are being applied with increasing



	AF	Non-AF Control	Odds retio (95% CI)	P value
Group1 (WGRS < 2.23)	43 (30.7)	97 (69.2)	1.00 (reference)	
Group2 (2.23≤ WGRS <3.37)	64 (46.3)	74 (53.6)	2.03 (1.24-3.39)	4.76×10^{-3}
Group3 (3.37≤ WGRS <4.17)	73 (52.1)	67 (47.8)	2.46 (1.46-3.97)	6.10×10^{-4}
Group4 (4.17≤ WGRS)	107 (68.5)	49 (31.4)	4.92 (3.08-8.70)	2.32×10^{-10}

Figure 2 Relationship between risk of atrial fibrillation (AF) and weighted genetic risk score (WGRS) in the screening cohort. Subjects of the screening cohort were stratified according to WGRS into quartile groups (groups 1–4). The ratio of AF to non-AF controls increased progressively with higher quartile, and there was a 4.92-fold increase in AF risk from the lowest to highest WGRS. CI = confidence interval.

frequency in general practice. Nonetheless, early AF detection still is challenging, especially in asymptomatic patients, so identifying patients at high risk for AF development based on genetic and other clinical factors is equally important for reducing cardiovascular and stroke-related morbidity and mortality.

Both environmental and genetic factors contribute to AF risk.[17] Previous large-scale association, GWAS, and meta-analyses have identified numerous SNPs associated with AF occurrence.[11,16,18,19]) In 2017, a GWAS by Low et al[10] identified 6 novel SNPs specifically associated with AF in a Japanese cohort (*KCND3*, *PPFIA4*, *SLC1A4-CEP68*, *HAND2*, *NEBL,* and *SH3PXD2A*). In the present study, we genotyped all 26 SNPs reported in previous GWASs. Because patient characteristics differed significantly between AF patients and non-AF controls in the screening cohort, we performed propensity score methods for adjustment of confounding factors. We found that 5 SNPs were associated with AF after Bonferroni correction: *PRRX1* (rs3903239), *ZFHX3* (rs2106261), *PTIX2* (rs6817105), *HAND2* (rs7698692), and *NEURL1* (rs60572254), and the odds ratios were equal to or higher than reported in a previous GWAS.[20,21]

Muse et al[22] calculated the WGRSs of 12 AF-associated loci (rs13376333 [*KCNN3*], rs3903239 [*PRRX1*], rs10033464 [*PITX2*], rs17570669 [*PITX2*], rs2200733 [*PITX2*], rs3853445 [*PITX2*], rs3807989 [*CAV1*], rs10821415 [*C9orf3*], rs10824026 [*SYNPO2L*], rs1152591 [*SYNE2*], rs7164883 [*HCN4*], and rs2106261 [*ZFHX3*]) and found a 3-fold difference between the highest and lowest

Table 3 Clinical characteristics of study subjects in the replication cohort

Variable	All subjects (N = 1018)	AF group (N = 273)	Non-AF group (N = 745)	*P* value
Age (y)	46.9 ± 13.5	52.7 ± 11.3	44.6 ± 14.2	3.46×10^{-24}
Male	617 (60.6)	205 (75.1)	412 (55.3)	4.52×10^{-13}
BMI	22.7 ± 3.3	24.1 ± 3.4	22.4 ± 3.2	6.13×10^{-17}
Hypertension	275 (27.0)	121 (44.3)	154 (20.6)	2.78×10^{-12}
Diabetes	74 (7.3)	35 (12.8)	39 (5.2)	2.08×10^{-7}
WGRS	3.21 ± 1.17	3.79 ± 1.18	2.89 ± 1.20	3.58×10^{-13}

Values are given as mean ± standard deviation or n (%) unless otherwise indicated.
AF = atrial fibrillation; BMI = body mass index; WGRS = weighted genetic risk score.

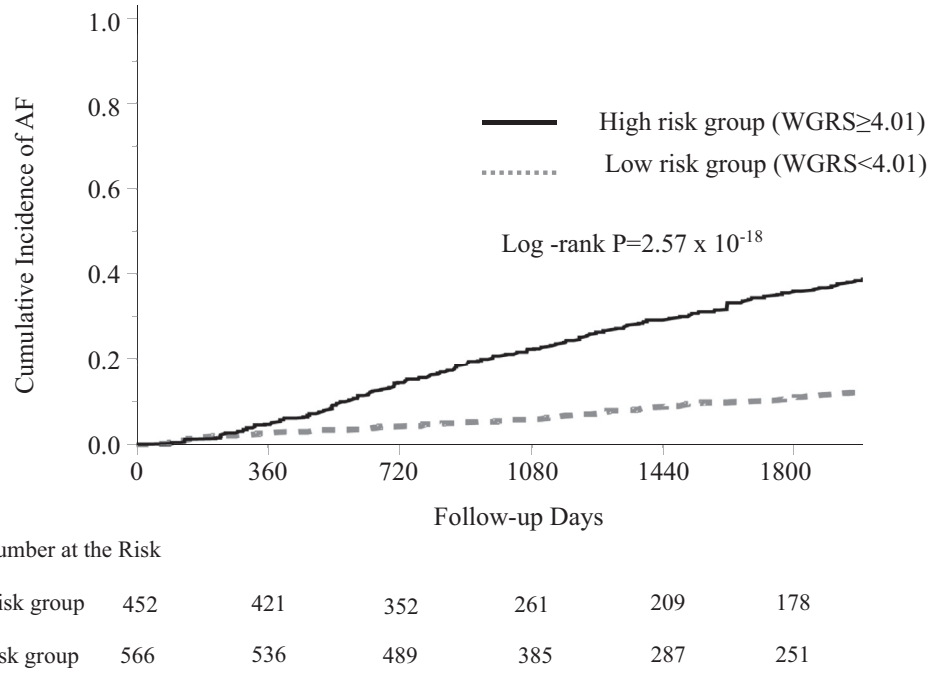


Figure 3 Cumulative incidence of atrial fibrillation (AF) in the replication cohort. Stratification of cumulative AF risk groups according to the weighted genetic risk score (WGRS). Subjects with WGRS ≥4.01 were defined as the high-risk group for AF, whereas those with WGRS <4.01 were classified as the low-risk group. The high-risk group demonstrated a significantly greater AF incidence (40.9% vs 16.1%; log-rank $P = 2.57 \times 10^{-18}$).

quintiles after adjusting for other clinical risk factors (age, sex, BMI, hypertension, and diabetes). In this study, we calculated the WGRS of the 5 identified AF-associated SNPs using logistical regression analysis and found a 4.9-fold difference in AF risk between the highest and lowest WGRS. We also found that WGRS was able to predict AF occurrence more accurately than any single SNP. In addition, we prospectively validated the accuracy of WGRS for AF prediction in a replication cohort by ROC analysis and found results consistent with the screening cohort.

Logistic multivariate analysis revealed that WGRS was independently associated with AF occurrence. According to the Danish Twin Registry study, genetic factors account for 62% of the variation in AF risk and environmental factors for 38%.[23] Said et al[24] reported that combining GRS and lifestyle risk factors (smoking, BMI, and physical activity) yielded greater AF prediction accuracy among the UK Biobank cohort. Poor lifestyle was associated with HR up to 5.41 for AF in the high genetic risk group.[24] Weng et al[25] demonstrated contributions from both genetic and clinical factors in determining long-term AF risk in a European percipient sample from the community-based Framingham Heart Study, with estimated incidence ranging from about 20% among individuals in the lowest tertiles of polygenic and clinical risk to about 50% in the highest tertiles.

We constructed a predictive logistic model combining WGRS and weighted AF clinical risk factors (age, BMI, sex, and hypertension) in Japanese cohorts and found better discrimination of AF by ROC analysis (AUC 0.84) compared to ROC analysis of WGRS alone, in accordance with the reported importance of environmental factors in AF onset. The genetic score on its own was inferior to clinical risk model, but the additive model is significantly better than clinical model. In our study, however, the incidence of AF was higher than in previous studies because the participants were elderly high-risk outpatients at the department of cardiovascular medicine. We used the traditional nongenetic AF risk factors (age, sex, obesity, hypertension, and diabetes) previously reported in the Japanese large-scale cohort study. However, we could not obtain enough data about history of drinking and smoking, presence of dyslipidemia, and medication from the medical records, which may have influenced overall accuracy.[14] Thus, additional studies are required to assess the predictive accuracy of this model in the general Japanese adult population.

Table 4 Multivariate analysis of occurrence of AF in the replication cohort

Variable	HR (95% CI)	*P* value
Age >50 y	3.42 (2.35–4.96)	9.95×10^{-11}
Male	2.38 (1.67–3.42)	1.86×10^{-6}
BMI >25 kg/m^2	2.53 (1.77–3.58)	2.56×10^{-7}
Hypertension	1.63 (1.14–2.31)	6.52×10^{-3}
Diabetes	1.49 (0.84–2.65)	.16
WGRS >4.01	3.27 (2.37–4.52)	6.72×10^{-13}

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; HR = hazard ratio; WGRS = weighted genetic risk score.

Study limitations

First, the propensity score matching necessary to reduce the selection bias in the screening cohort markedly reduced the

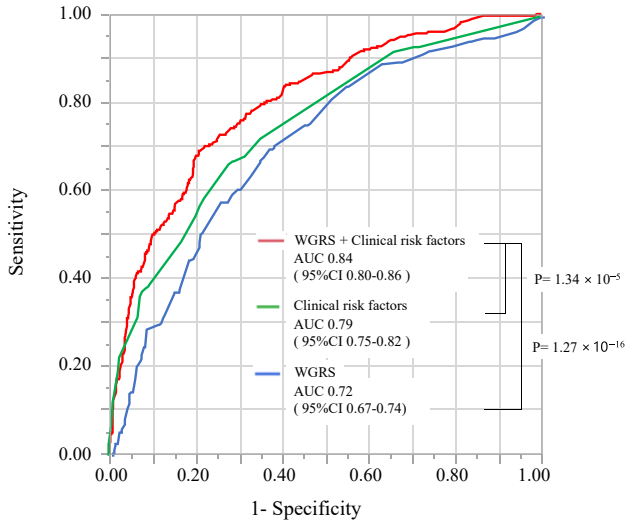


Figure 4 Receiving operating characteristic analysis of the weighted genetic risk score (WGRS) prediction model and the combined prediction model including WGRS and weighted clinical risk factors in the replication cohort. Receiver operating characteristic analysis of WGRS yielded an area under the curve (AUC) of 0.72, sensitivity 65.4%, and specificity 69.6%. Respective values for weighted clinical risk score (CRS) (age >50 years, body mass index >25 kg/m^2, sex, and hypertension) were 0.79, 70.9%, and 74.3%. A combined predictive logistical model was constructed by combining WGRS and CRS. This model yielded better discrimination of AF (AUC 0.84; sensitivity 75.4%; specificity 80.2%) than either WGRS or CRS alone. CI = confidence interval.

sample size. Therefore, this new combined risk model for AF must be further validated using a larger prospective cohort recruited from multiple centers. Second, this study did not consider differences in medication history among subjects, which may have influenced overall accuracy. Third, AF in this study was confirmed by 12-lead electrocardiography or portable electrocardiograph, so whether this model is sufficient for detecting asymptomatic AF is still uncertain. Fourth, the present study was performed in a Japanese population, so additional studies are needed to determine model applicability to other racial and ethnic groups.

Despite these limitations, this is the first AF prediction model constructed using both the WGRS of 5 strongly AF-associated SNPs and clinical risk factors with validation in the Japanese population. Our results suggest that this combined model may be useful for early AF detection and intervention.

Conclusion

The combination risk model using AF-associated SNPs (rs3903239, rs2106261, rs6817105, rs7698692, and rs6057225) and clinical risk factors (age, hypertension, BMI, and sex) can stratify AF risk in the Japanese population more accurately than either WGRS or clinical factors alone.

Acknowledgments

We thank the clerical and medical staff at Hiroshima University Hospital for their assistance.

Appendix A

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.01.006.

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