A Genetic Risk Score for Atrial Fibrillation Predicts the Response to Catheter Ablation

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Atrial fibrillation – heritable disorder

✓ Genetic variation is an important determinant of susceptibility to AF
✓ Many genetic variations reported to be associated with AF
   - influences several biological pathway
   - modifies the patient’s susceptibility to AF in a complex trait

Cardiogenesis

Cell architecture and coupling

Ion channels

Primitve ventricle

GATA4
GATA5
GATA6
GREM2
NKX2-5
NKX2-6
PTX2
ZFHx3
PRRX1
NEURAL
TBX5
CAND2

GJA1
GJA5
LMNA
NUP155
MYOC1
SYNE2
CAV1

SCN1B
SCN2B
SCN5B
SCN4B
SCN5A
SCN10A
HCN4

KCNJ5
KCNJ3
KCNJ1
KCNJ2
KCNJ8
KCNJ9
KCNB1
KCNB2
KCNN2
KCNN4
Ryr2
Abcc6

Sinus rhythm

Atrial fibrillation
Clinical application of AF-associated genetic variations

Genetic screening to identify the individuals at risk for AF

→ **Limited implication in clinical practice**

  ✓ lack of robust prediction model applicable to general populations
  ✓ lack of effective interventions that can prevent AF or diminish the AF burden

Prediction model of clinical response to AF treatment

  ✓ may help appropriate selection of candidates to invasive procedures
  ✓ individualizing the treatment strategies
  ✓ enhance our understanding of the mechanism of disease progression
Objectives of the study

- To perform a comprehensive analysis on the relationship between **AF-associated common genetic variants** and long-term **clinical outcome of AF ablation**

- To construct a predictive **Genetic Risk Score**, based on AF-associated common genetic variants
Study design

Enrollment

Consecutive enrollment of paroxysmal / persistent AF undergoing RFCA

Clinical assessment

Genotyping for 20 AF-susceptibility SNPs

Catheter ablation

Regular follow-up 1/3/6M and every 3-6M

SNP selection and Genetic Risk Score (GRS) construction

Genotyping and RFCA

Clinical follow-up

Analysis of clinical outcomes according to GRS

Analysis
Methods

Patient inclusion
• From 2 centers with AF ablation cohort
• Consecutive enrollment of patients who underwent RFCA
  ✓ June 2008 ~ March 2015
  ✓ de novo or repeat procedure for paroxysmal and persistent AF

Ablation procedure
• EGM recording by Prucka CardioLab EP Recording System
• Ablation was guided by 3D electro-anatomical mapping
• Specific ablation procedure was left to the discretion of the clinician

Genotyping
• Performed for top 20 AF-susceptibility SNPs
• Genomic DNA : whole blood sample
• SNP genotyping : TaqMan® assay, Applied Biosystems™
| SNP       | Loci | Nearest Gene | AF Associated Risk / Other Allele | Risk Allele Frequency | Risk Estimates from the Literature |
|-----------|------|--------------|-----------------------------------|-----------------------|-----------------------------------|
| rs6666258 | 1q21 | KCNN3        | C/G                               | 0.980                 | 1.18                              |
| rs13376333| 1q21 | KCNN3        | T/C                               | 0.019                 | 1.56                              |
| rs3903239 | 1q24 | PRRX1        | G/A                               | 0.609                 | 1.14                              |
| rs4642101 | 3p25 | CAND2        | G/T                               | 0.237                 | 1.10                              |
| rs1448818 | 4q25 | PITX2        | C/A                               | 0.376                 | 1.14                              |
| rs6817105 | 4q25 | PITX2        | C/T                               | 0.696                 | 1.64                              |
| rs2200733 | 4q25 | PITX2        | T/C                               | 0.693                 | 1.72                              |
| rs4400058 | 4q25 | PITX2        | A/G                               | 0.157                 | 1.18                              |
| rs6843082 | 4q25 | PITX2        | G/A                               | 0.863                 | 2.03                              |
| rs6838973 | 4q25 | PITX2        | C/T                               | 0.536                 | 1.21                              |
| rs13216675| 6q22 | GJA1         | T/C                               | 0.653                 | 1.10                              |
| rs3807989 | 7q31 | CAV1         | G/A                               | 0.712                 | 1.14                              |
| rs10821415| 9q22 | C9orf3       | A/C                               | 0.293                 | 1.13                              |
| rs10824026| 10q22| SYNPO2L      | A/G                               | 0.556                 | 1.17                              |
| rs12415501| 10q24| NEURL        | T/C                               | 0.169                 | 1.18                              |
| rs6490029 | 12q24| CUX2         | A/G                               | 0.725                 | 1.12                              |
| rs10507248| 12q24| TBX5         | T/G                               | 0.485                 | 1.11                              |
| rs1152591 | 14q23| SYNE2        | A/G                               | 0.337                 | 1.13                              |
| rs7164883 | 15q24| HCN4         | G/A                               | 0.111                 | 1.16                              |
| rs2106261 | 16q22| ZFHX3        | T/C                               | 0.452                 | 1.24                              |
Methods

Genetic Risk Score (GRS) construction

• Selection of candidate SNP:
  SNPs showing at least borderline significant association ($P < 0.10$) with AF recurrence in cross-sectional analysis

• Unknown effect size → additive, unweighted model:
  \[
  \text{Genetic Risk Score} = \text{total number of risk alleles of selected candidate SNPs}
  \]

Primary outcome

• Recurrence of atrial tachyarrhythmia after catheter ablation
  - Any documented episode of AF, atrial flutter or atrial tachycardia lasting $>30$ sec after a 3-month blanking period
Baseline characteristics of study population

|                                | Total Cohort (N = 746) |
|--------------------------------|-------------------------|
| **Age, y**                     | 59.4±10.6               |
| **Male sex, %**                | 73.5%                   |
| **BMI, kg/m²**                 | 24.8±2.8                |
| **Paroxysmal AF, %**           | 56.3%                   |
| **Hypertension, %**            | 48.1%                   |
| **Diabetes mellitus, %**       | 15.4%                   |
| **Heart failure, %**           | 12.2%                   |
| **History of stroke, %**       | 5.2%                    |

**Echocardiography**

|                                |                         |
|--------------------------------|-------------------------|
| **LA dimension, mm**           | 42.5±6.4                |
| **LA volume index, mL/m²**     | 42.5±15.9               |
| **LVEDD, mm**                  | 49.3±6.2                |
| **IVSd, mm**                   | 9.4±1.9                 |
| **LVEF, %**                    | 62.6±8.0                |
Clinical outcomes

| Outcomes                              | Total Cohort (N = 746) |
|---------------------------------------|------------------------|
| **Median follow-up, days**            | 684 (324-1205)         |
| **Recurrence**                        |                        |
| within blanking period, %             | 21.4%                  |
| within 6-month, %                     | 8.2%                   |
| within 12-month, %                    | 14.7%                  |
| **Type of recurrence**                |                        |
| Atrial fibrillation, %                | 57.1%                  |
| Atrial flutter or atrial tachycardia, % | 42.9%                  |

**Definition of recurrence**

Any documented episode of **AF, atrial flutter or atrial tachycardia** lasting >30 sec after a **3-month blanking period**
| SNP          | Loci | Nearest Gene | Risk Allele | Recurrent AF† | OR       | P value |
|--------------|------|--------------|-------------|---------------|----------|---------|
| rs6666258    | 1q21 | KCNN3        | C           |               | 2.579    | (0.786-8.465) | 0.118   |
| rs13376333   | 1q21 | KCNN3        | T           |               | 0.385    | (0.115-1.289)  | 0.122   |
| rs3903239    | 1q24 | PRRX1        | G           |               | 1.077    | (0.841-1.380)  | 0.555   |
| rs4642101    | 3p25 | CAND2        | G           |               | 0.747    | (0.554-1.009)  | 0.057   |
| rs1448818    | 4q25 | PITX2        | C           |               | 1.240    | (0.971-1.583)  | 0.085   |
| rs6817105    | 4q25 | PITX2        | C           |               | 1.405    | (1.075-1.837)  | 0.013   |
| rs2200733    | 4q25 | PITX2        | T           |               | 1.430    | (1.093-1.871)  | 0.009   |
| rs4400058    | 4q25 | PITX2        | A           |               | 0.816    | (0.576-1.155)  | 0.251   |
| rs6843082    | 4q25 | PITX2        | G           |               | 1.438    | (0.988-2.092)  | 0.058   |
| rs6838973    | 4q25 | PITX2        | C           |               | 1.269    | (0.978-1.648)  | 0.073   |
| rs1321675    | 6q22 | GJA1         | T           |               | 1.010    | (0.782-1.305)  | 0.939   |
| rs3807989    | 7q31 | CAV1         | G           |               | 1.010    | (0.773-1.318)  | 0.944   |
| rs10821415   | 9q22 | C9orf3       | A           |               | 0.946    | (0.720-1.244)  | 0.691   |
| rs10824026   | 10q22 | SYNPO2L    | A           |               | 0.917    | (0.723-1.164)  | 0.477   |
| rs12415501   | 10q24 | NEURL       | T           |               | 1.173    | (0.859-1.602)  | 0.314   |
| rs6490029    | 12q24 | CUX2        | A           |               | 0.818    | (0.626-1.070)  | 0.142   |
| rs10507248   | 12q24 | TBX5        | T           |               | 0.956    | (0.754-1.213)  | 0.713   |
| rs1152591    | 14q23 | SYNE2       | A           |               | 0.934    | (0.726-1.200)  | 0.593   |
| rs7164883    | 15q24 | HCN4        | G           |               | 1.231    | (0.856-1.772)  | 0.263   |
| rs2106261    | 16q22 | ZFHX3       | T           |               | 1.289    | (1.007-1.652)  | 0.044   |

† Association was tested with unadjusted logistic regression model.
| SNP         | Loci  | Nearest Gene | Risk Allele | Recurrent AF† | Inclusion in GRS |
|-------------|-------|--------------|-------------|--------------|------------------|
| rs6666258   | 1q21  | KCNN3        | C           | 2.579 (0.786-8.465) | 0.118            |
| rs13376333  | 1q21  | KCNN3        | T           | 0.385 (0.115-1.289) | 0.122            |
| rs3903239   | 1q24  | PRRX1        | G           | 1.077 (0.841-1.380) | 0.555            |
| rs4642101   | 3p25  | CAND2        | G           | 0.747 (0.554-1.009) | 0.057            |
| rs1448818   | 4q25  | PITX2        | C           | 1.240 (0.971-1.583) | 0.085            |
| rs6817105   | 4q25  | PITX2        | C           | 1.405 (1.075-1.837) | 0.013            |
| rs2200733   | 4q25  | PITX2        | T           | 1.430 (1.093-1.871) | 0.009            |
| rs4400058   | 4q25  | PITX2        | A           | 0.816 (0.576-1.155) | 0.251            |
| rs6843082   | 4q25  | PITX2        | G           | 1.438 (0.988-2.092) | 0.058            |
| rs6838973   | 4q25  | PITX2        | C           | 1.269 (0.978-1.648) | 0.073            |
| rs13216675  | 6q22  | GJA1         | T           | 1.010 (0.782-1.305) | 0.939            |
| rs3807989   | 7q31  | CAV1         | G           | 1.010 (0.773-1.318) | 0.944            |
| rs10821415  | 9q22  | C9orf3       | A           | 0.946 (0.720-1.244) | 0.691            |
| rs10824026  | 10q22 | SYNPO2L      | A           | 0.917 (0.723-1.164) | 0.477            |
| rs12415501  | 10q24 | NEURL        | T           | 1.173 (0.859-1.602) | 0.314            |
| rs6490029   | 12q24 | CUX2         | A           | 0.818 (0.626-1.070) | 0.142            |
| rs10507248  | 12q24 | TBX5         | T           | 0.956 (0.754-1.213) | 0.713            |
| rs1152591   | 14q23 | SYNE2        | A           | 0.934 (0.726-1.200) | 0.593            |
| rs7164883   | 15q24 | HCN4         | G           | 1.231 (0.856-1.772) | 0.263            |
| rs2106261   | 16q22 | ZFHX3        | T           | 1.289 (1.007-1.652) | 0.044            |

† Association was tested with unadjusted logistic regression model.
Construction of Genetic Risk Score (GRS)

- **Unweighted, additive model**
  
  \[ \text{Genetic Risk Score} = \text{the sum of the number of risk alleles} \ (5 \text{ selected SNPs}) \]

- **Distribution of Genetic Risk Score**

| Total cohort | Grouped according to recurrence |
|--------------|---------------------------------|
| ![](chart1.png) | ![](chart2.png) |

| GRS (mean±SD) |  |
|---------------|---|
| Without Recurrence | 5.7 ± 1.8 |
| With Recurrence | 6.3 ± 1.7 |

\( P < 0.001 \)
Association of GRS and AF recurrence

✓ **Genetic risk score** was significantly associated with recurrent AF

**HR**^*^ 1.14 (95% CI 1.04-1.24, *P* = 0.006)

| Variables                                      | Recurrent AF†   |
|-----------------------------------------------|-----------------|
|                                               | Hazard ratio    | P value |
| Genetic Risk Score                            | 1.135 (1.036-1.244) | 0.006   |
| Age                                           | 0.997 (0.981-1.013) | 0.677   |
| Male                                          | 1.201 (0.811-1.779) | 0.361   |
| Persistent AF (opposed to paroxysmal AF)     | 1.209 (0.875-1.670) | 0.249   |
| LA size                                       | 1.060 (1.036-1.085) | <0.001  |
| Hypertension                                  | 0.757 (0.550-1.042) | 0.088   |

† Association was tested with Cox proportional hazards model, adjusted for age, sex, hypertension, persistent as opposed to paroxysmal AF, and LA size.
Association of GRS and AF recurrence

**Grouped analysis**

Association was tested with Cox proportional hazards model, adjusted for age, sex, hypertension, persistent as opposed to paroxysmal AF, and LA size.

Hazard ratio was compared with the low risk group.
Subgroup analysis with subjects underwent \textit{de-novo} ablation

![Graph showing survival rates with different risk levels (Low Risk (GRS 0\textendash}3), Intermediate Risk (GRS 4\textendash}6), High Risk (GRS 7\textendash}10)). The Log Rank test yields a p-value of 0.002.]

| Number at Risk         | Low risk | 65 | 42 | 35 | 17 | 2 |
|------------------------|----------|----|----|----|----|---|
|                       | Intermediate risk | 248 | 156 | 108 | 56 | 23 |
|                       | High risk   | 197 | 129 | 85  | 40 | 9 |
Limitations

• Validation of the current genetic risk score model in an independent population is required.

• The panel of genetic variants may be incomplete.

• Cost-effectiveness analysis should be conducted to rationalize genetic-information guided approach in AF management.
Conclusions

• Genetic Risk Score could predict the recurrence after AF catheter ablation
  ✓ Addition of 1 risk allele increased the risk by 14%
  ✓ High-risk group (GRS 7~10) showed 2.6 times increased risk of AF recurrence, compared with low-risk group (GRS 0~3)

• Improving the prediction of clinical response to catheter ablation may help identification of proper candidates of AF catheter ablation.
Thank you for your attention