Role of Genetics in AF

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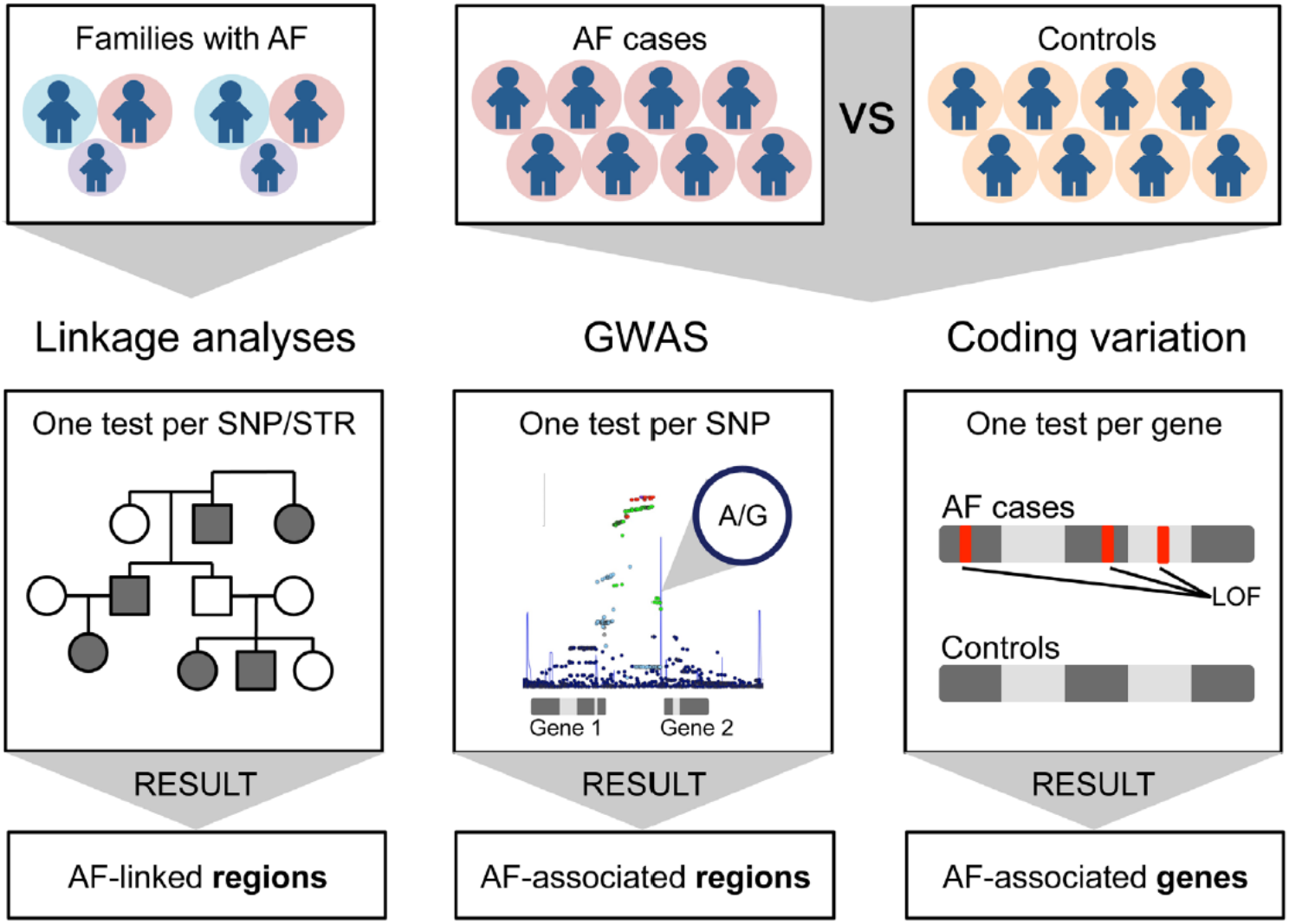
COI Disclosure

Hee Tae Yu

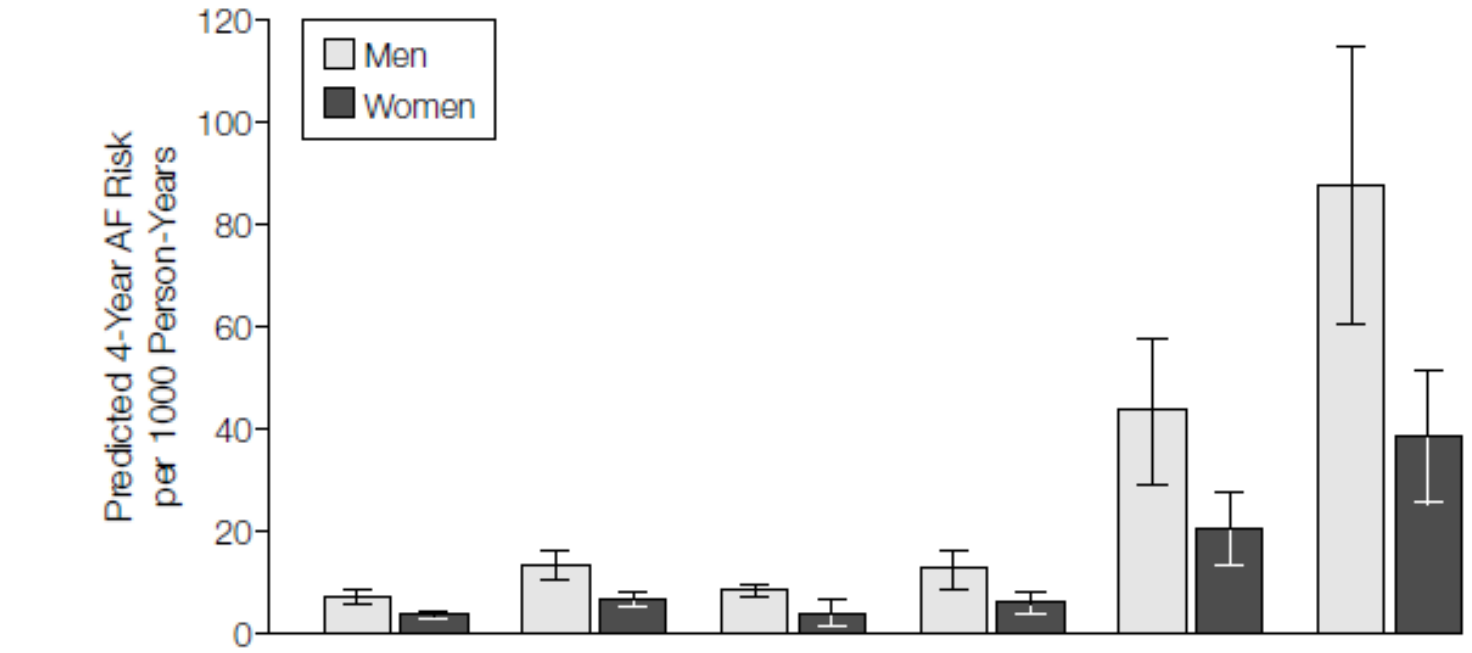
The authors have no financial conflicts of interest to disclose concerning the presentation

Three types of genetic analyses for AF



Roselli C et al. Circ Res 2020;127:21-33

Parental AF as a risk factor for AF in offspring



Risk Factor						
Hypertension	–	–	+	+	+	+
Diabetes Mellitus	–	–	–	+	+	+
Clinically Overt Heart Disease	–	–	–	–	+	+
Parental AF	–	+	–	–	–	+

Fox CS et al. JAMA 2004;291:2851-5

A first-degree family history in lone AF

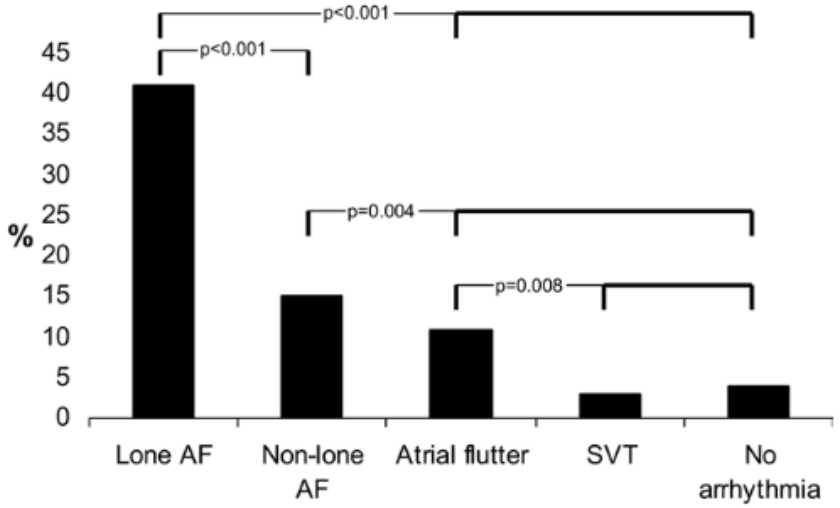


Figure 1 Proportions of patients in each group who reported having at least one first-degree family member with AF. *P*-values represent comparisons denoted by brackets in bold.

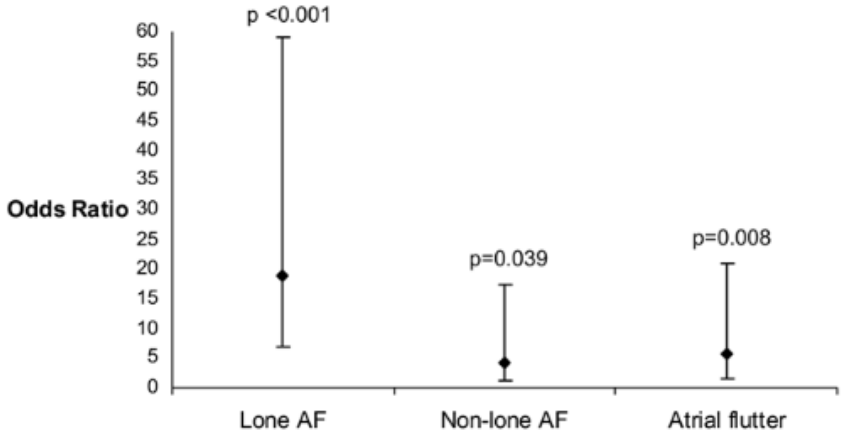


Figure 2 Odds ratios of having at least one first-degree relative with AF in the lone AF, non–lone AF, and atrial flutter groups compared with controls after adjusting for age, race, gender, and body mass index. Error bars denote 95% CIs.

Marcus GM et al. Heart Rhythm. 2008;5:826-30

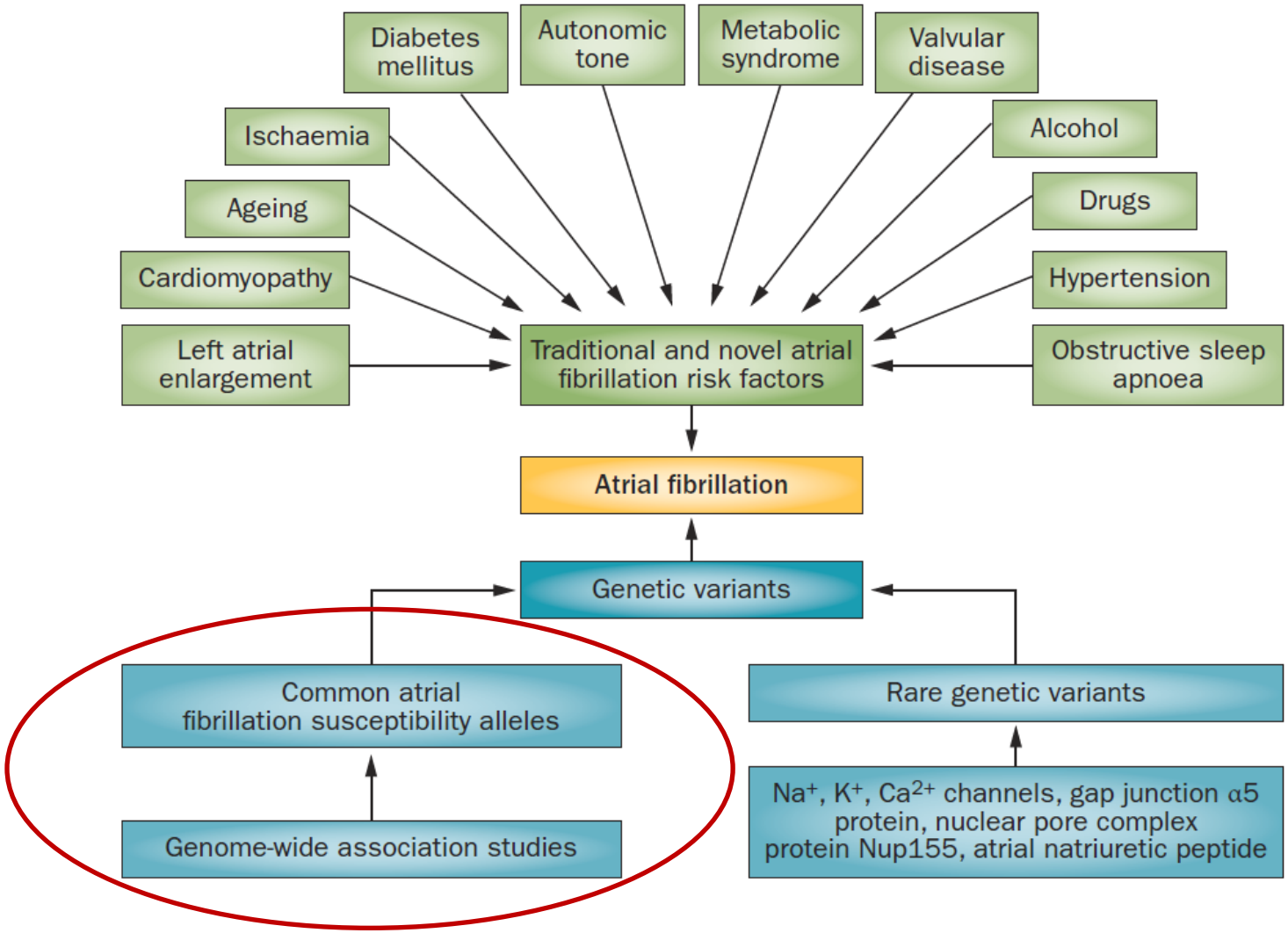
Rare genetic variants in AF

Gene	Official full name	Electrophysiological consequence
Ion channel gene		
ABCC9	ATP-binding cassette, subfamily C, member 9	LOF
HCN4	Hyperpolarization-activated cyclic nucleotide-gated 4 channel	LOF
KCNA5	Potassium voltage-gated channel subfamily A member 5	GOF or LOF
KCND3	Potassium voltage-gated channel subfamily D member 3	GOF
KCNE1	Potassium voltage-gated channel subfamily E regulatory subunit 1	GOF
KCNE2	Potassium voltage-gated channel subfamily E regulatory subunit 2	GOF
KCNE3	Potassium voltage-gated channel subfamily E regulatory subunit 3	GOF
KCNE5	Potassium voltage-gated channel subfamily E regulatory subunit 5	GOF
KCNH2	Potassium voltage-gated channel subfamily H member 2	GOF or LOF
KCNJ2	Potassium voltage-gated channel subfamily J member 2	GOF
KCNJ5	Potassium voltage-gated channel subfamily J member 5	GOF
KCNJ8	Potassium voltage-gated channel subfamily J member 8	GOF
KCNQ1	Potassium voltage-gated channel subfamily Q member 1	GOF
SCN1B	Sodium voltage-gated channel β subunit 1	GOF or LOF
SCN2B	Sodium voltage-gated channel β subunit 2	LOF
SCN3B	Sodium voltage-gated channel β subunit 3	LOF
SCN4B	Sodium voltage-gated channel β subunit 4	LOF
SCN5A	Sodium voltage-gated channel α subunit 5	GOF or LOF
SCN10A	Sodium voltage-gated channel α subunit 10	GOF or LOF
Nonion channel gene		
GATA4	GATA binding protein 4	LOF
GATA5	GATA binding protein 5	LOF
GATA6	GATA binding protein 6	LOF
GJA1	Gap junction protein α 1	LOF
GJA5	Gap junction protein α 5	LOF
GREM2	Gremlin 2, DAN family BMP antagonist	GOF
JPH2	Junctophilin 2	LOF
LMNA	Lamin A/C	Unknown
NPPA	Natriuretic peptide A	GOF
NUP155	Nucleoporin 155	LOF
NKX2.5	NK2 homeobox 5	Unknown
PITX2	Paired like homeodomain 2	LOF
RYR2	Ryanodine receptor 2	GOF

- Many variants in genes encoding ion channel subunits, cardiac gap junctions and signaling molecules have been identified in families with AF caused by a single gene (monogenic) and patients with lone AF.
- These variants are associated with large effect sizes, and their minor allele frequencies are below 0.5%.
- a shortened atrial refractory period, a lengthening of the atrial action potential duration (APD), which results in ectopic activity, or by causing impaired electrical cell-to-cell communication that creates a conduction heterogeneity as a substrate for the maintenance of AF.

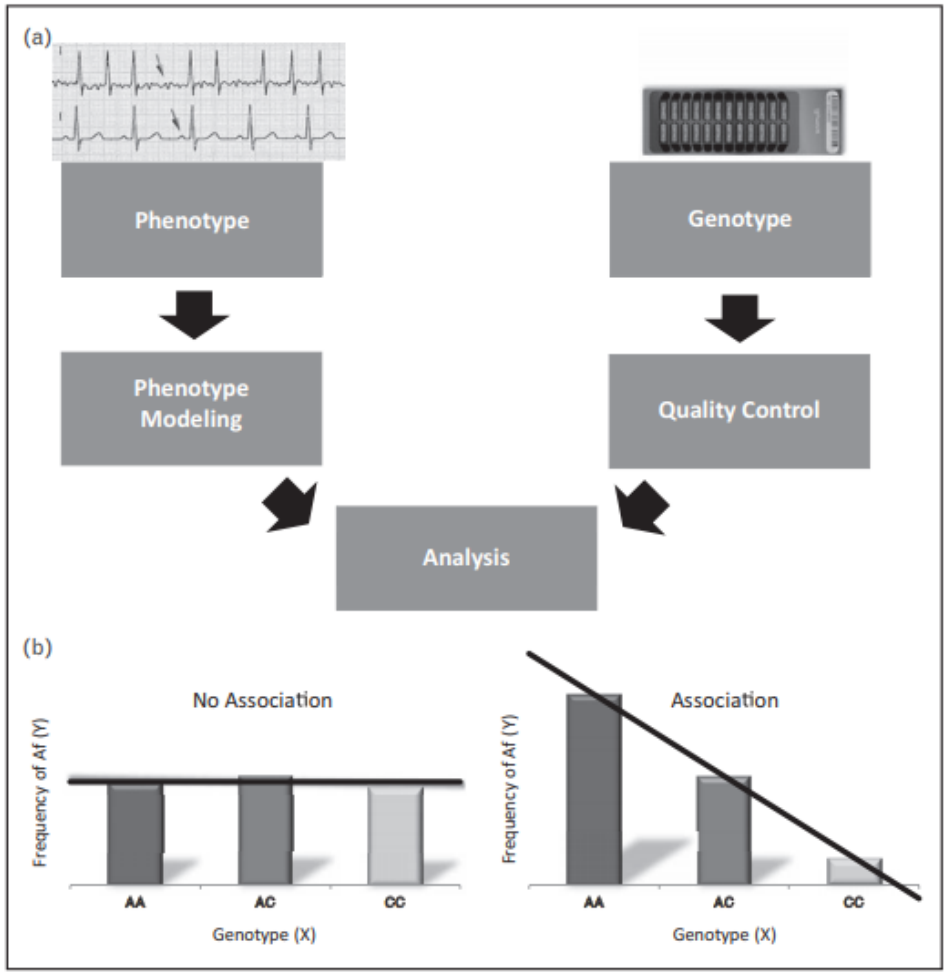
Hayashi K et al. Curr Opin Cardiol 2017;32:10-16

Clinical and Genetic Risk Factors for AF



Darbar and Roden. Nat Rev Cardiol 2013;10:317-29

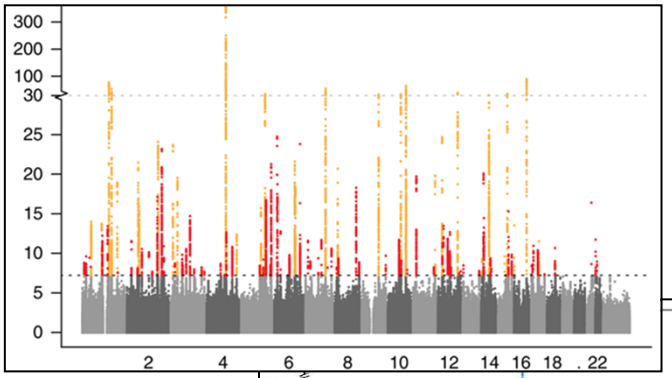
GWAS studies for common variants



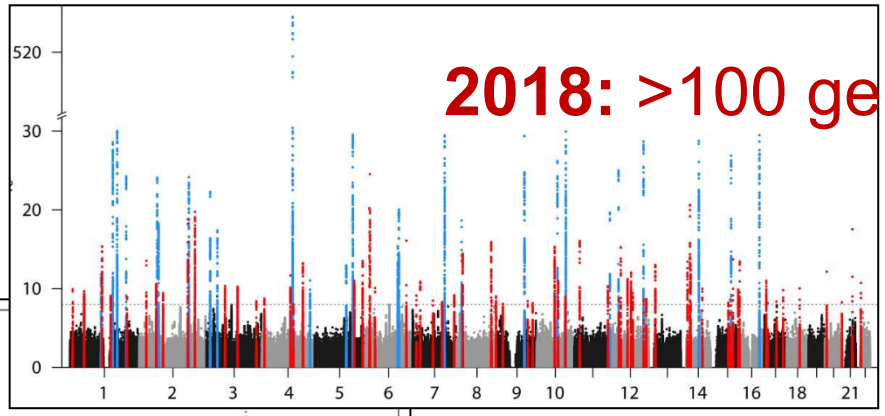
- Most atrial fibrillation cases fall into the category of common AF, with a variety of risk factors such as hypertension, diabetes, age, and valvular heart disease contributing to its pathogenesis.
- Whole-exome sequencing of patients with common AF has failed to show common or rare variation in genes implicated in familial AF.
- Instead, most variants associated with common AF with low or modest effect sizes, have been identified by Genome Wide Association Studies (GWAS) and fall in noncoding regions of the genome.

Hayashi K et al. Curr Opin Cardiol 2017;32:10-16

GWAS identifies common genetic variants associated with AF

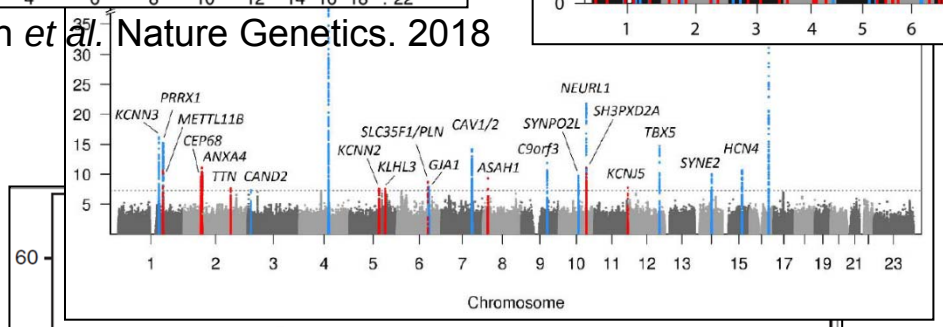


Nielsen *et al.* Nature Genetics. 2018



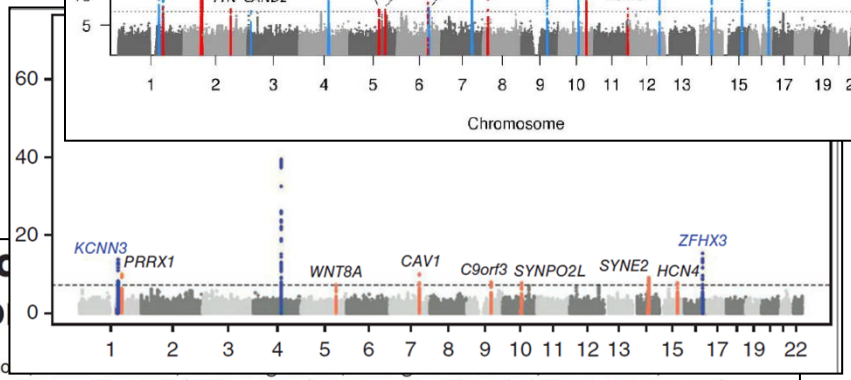
2018: >100 genetic loci

Roselli *et al.* Nature Genetics. 2018



2017: 23 genetic loci

Christophersen *et al*. Nature Genetics. 2017



2012: 10 genetic loci

Ellinor *et al*. Nature Genetics. 2012

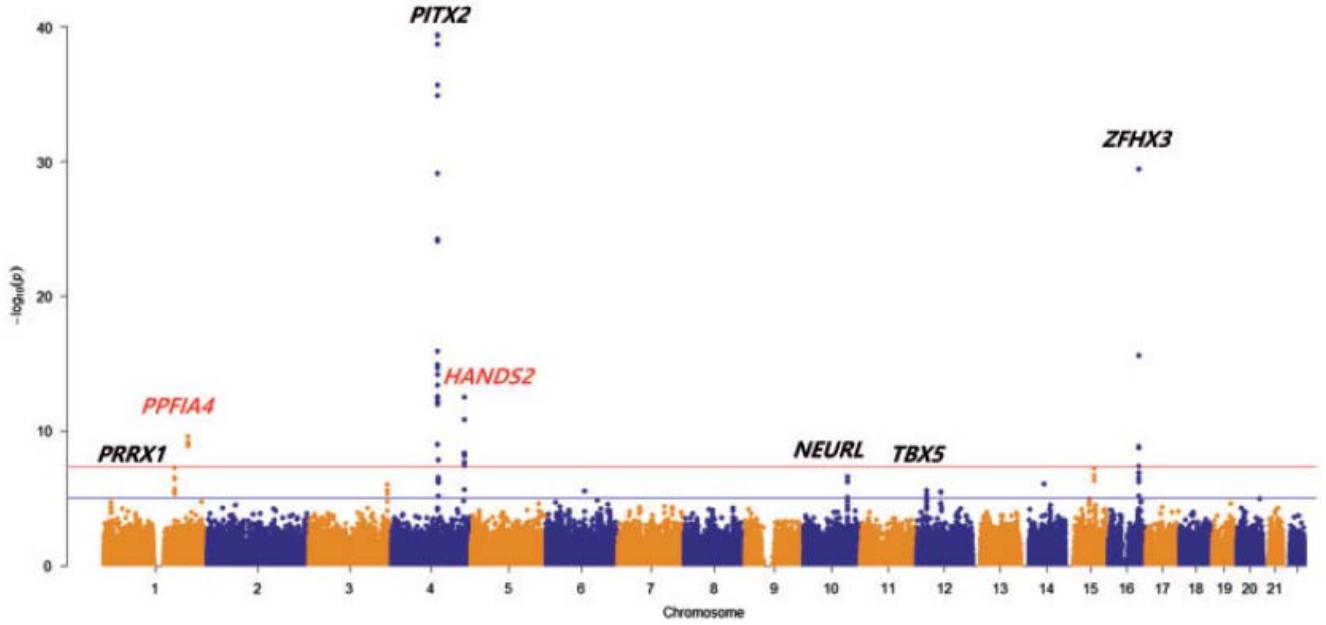
2007: 1 genetic locus

Gudbjartsson *et al*. Nature. 2007

GWAS Study in Korea

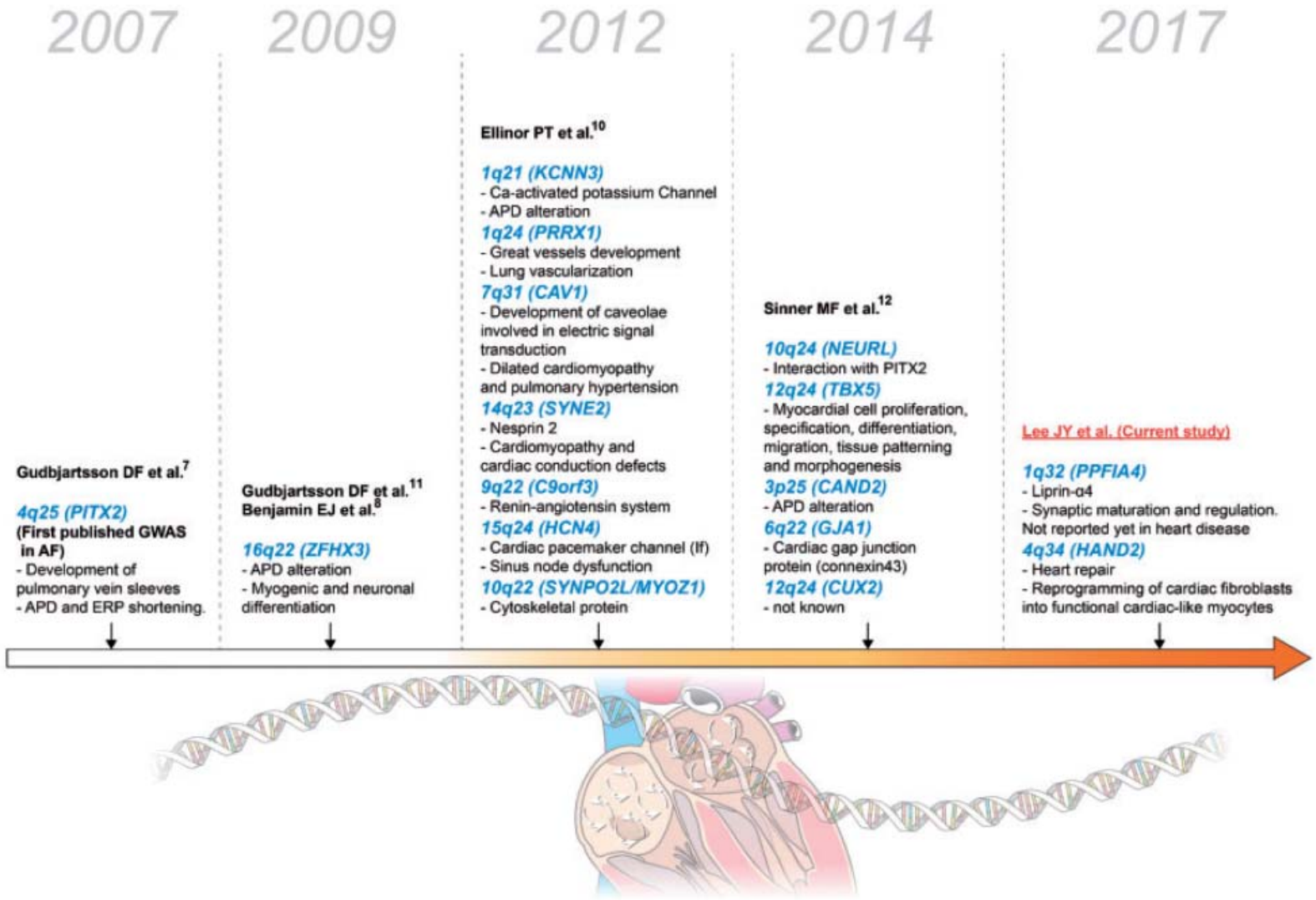
Korean atrial fibrillation network genome-wide association study for early-onset atrial fibrillation identifies novel susceptibility loci

Ji-Young Lee[1,2†], Tae-Hoon Kim[1†], Pil-Sung Yang[1], Hong Euy Lim[3], Eue-Keun Choi[4], Jaemin Shim[5], Eunsoon Shin[6], Jae-Sun Uhm[1], Jin-Seok Kim[3], Boyoung Joung[1], Seil Oh[4], Moon-Hyoung Lee[1], Young-Hoon Kim[5], and Hui-Nam Pak[1,2*]



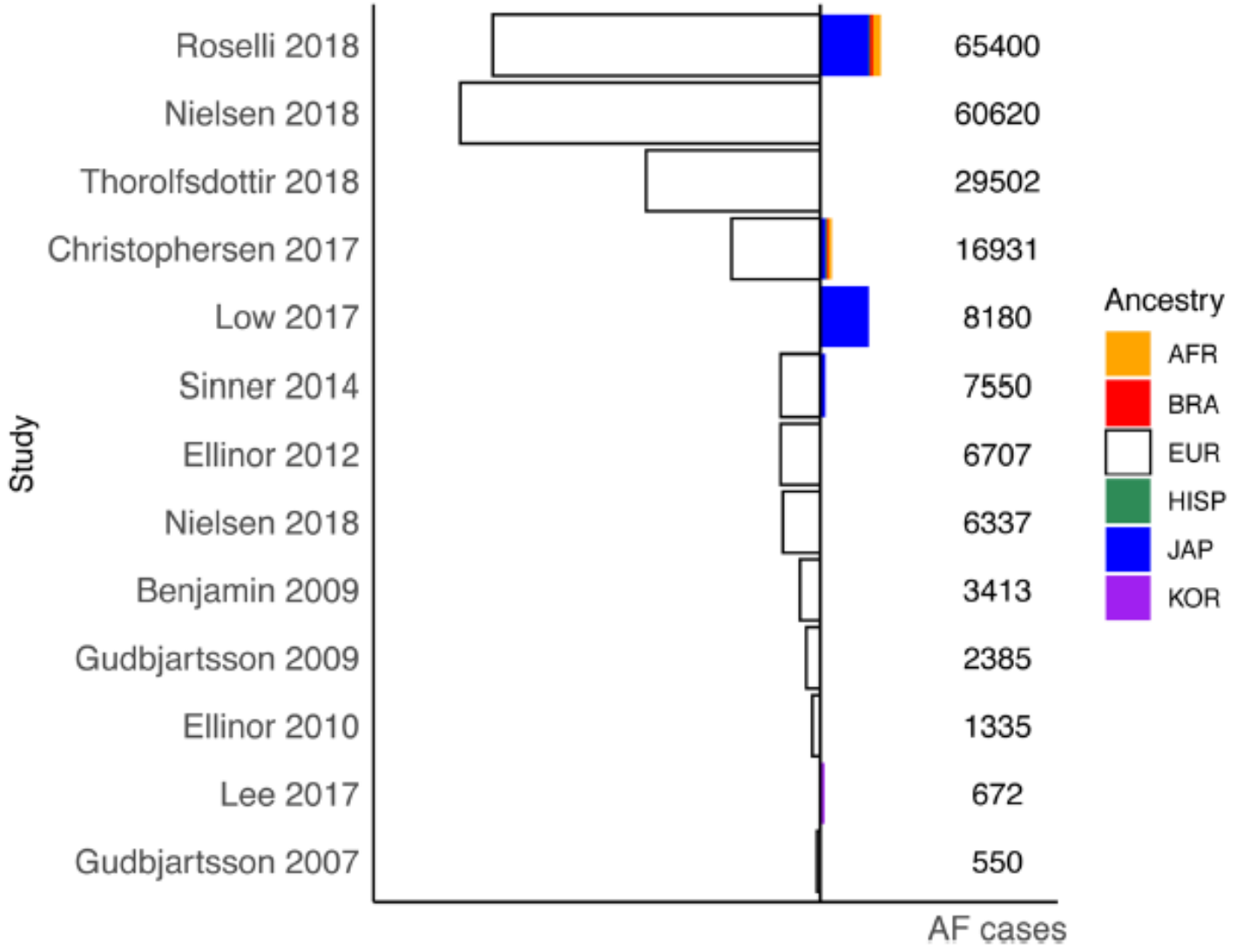
Lee JY, Kim TH, Pak HN et al. Eur Heart J 2017;38:2586–2594

GWAS Study in Korea



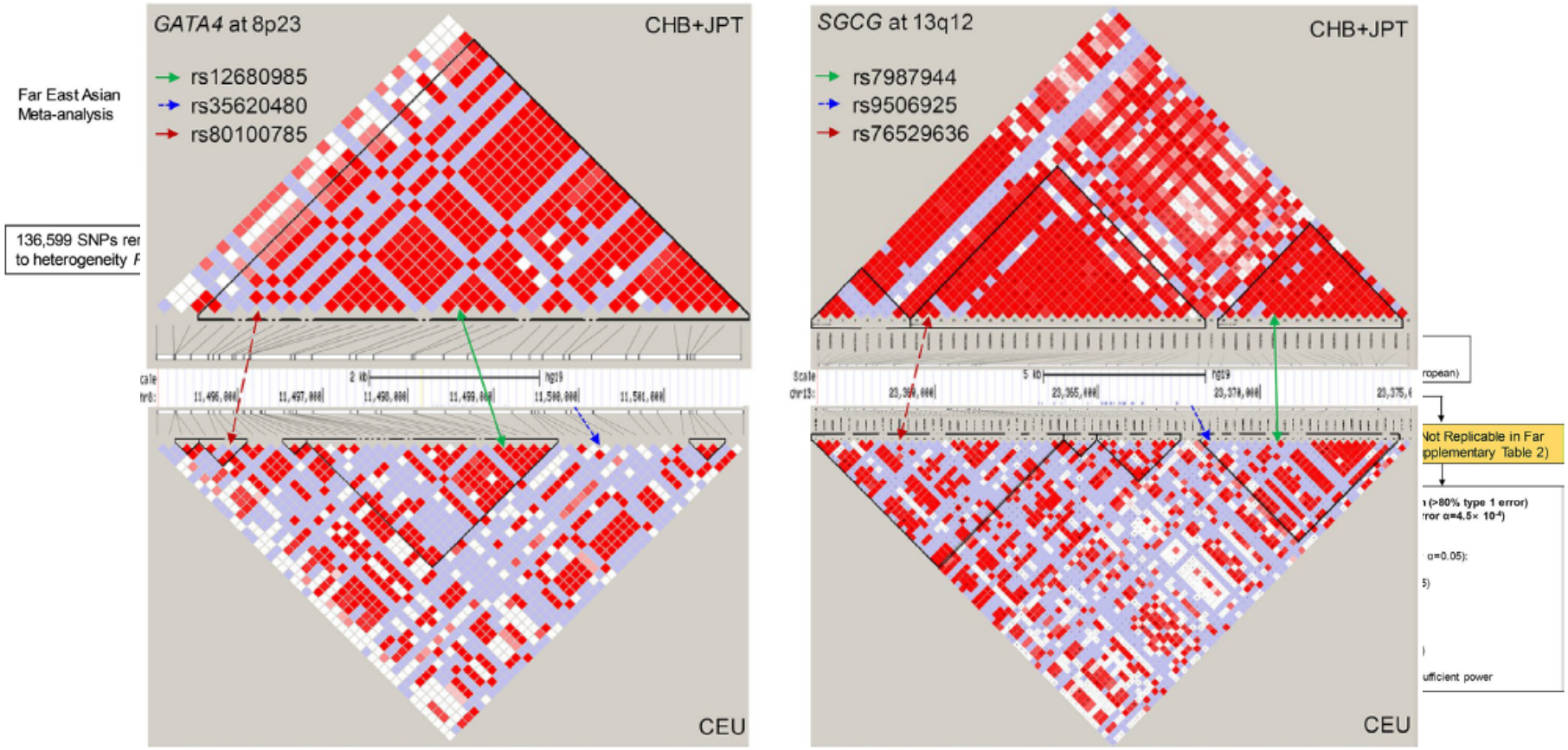
Lee JY, Kim TH, Pak HN et al. Eur Heart J 2017;38:2586–2594

Ancestry of the cases in GWAS for AF



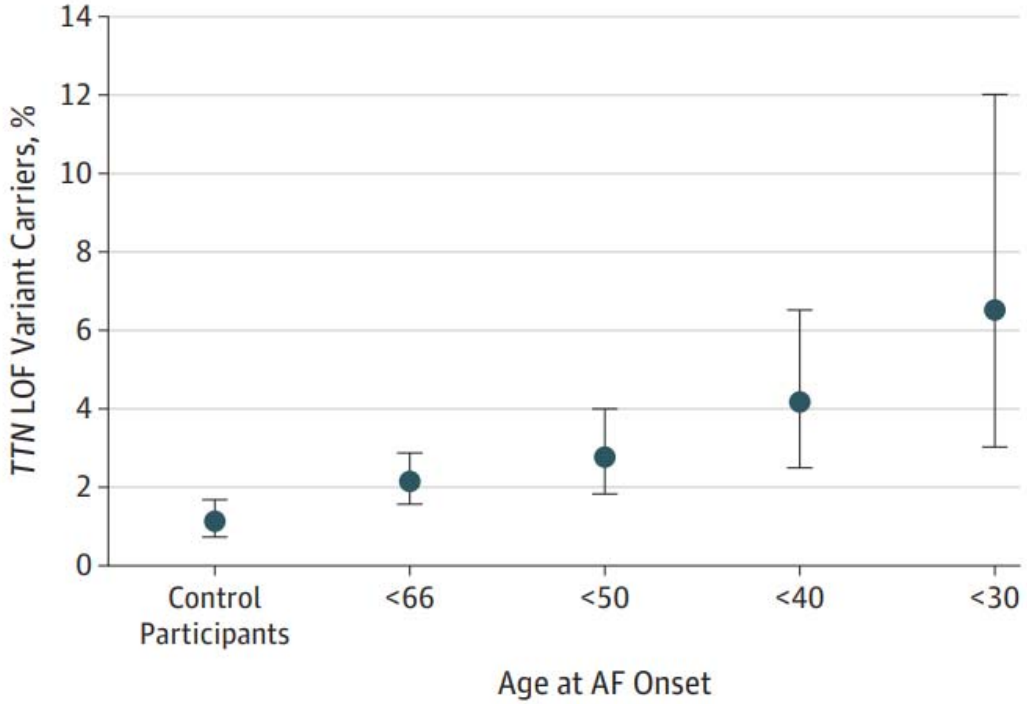
Reproducibility of European AF-associated SNPs in the East Asian GWAS meta-analysis

Ethnic similarities in genetic polymorphisms associated with atrial fibrillation: Far East Asian vs European populations



Hong M, Pak HN, et al. Eur J Clin Invest 2021;e13584

TTN loss of function mutations in early-onset AF
: Whole Genome sequencing



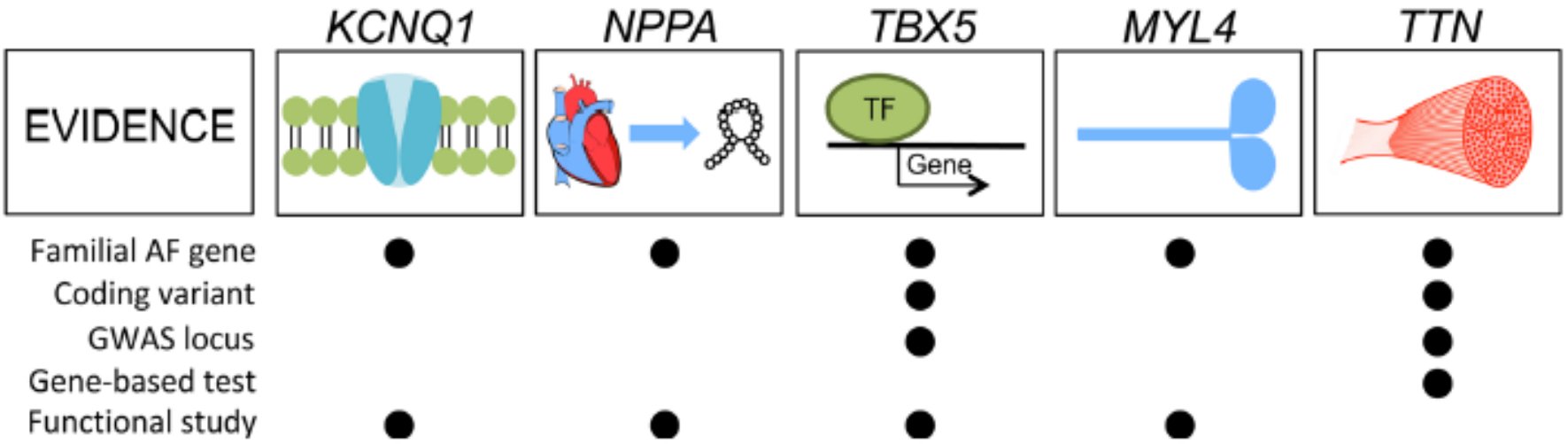
No. of participants					
TTN LOF carriers	24	44	27	18	9
Total participants	2116	2047	976	431	138

2800
AF cases
+
5000
controls

TTN LOF in AF onset <30 yrs
OR 5.94 (95% CI 2.64-13.36)
$p=1.64 \times 10^{-5}$

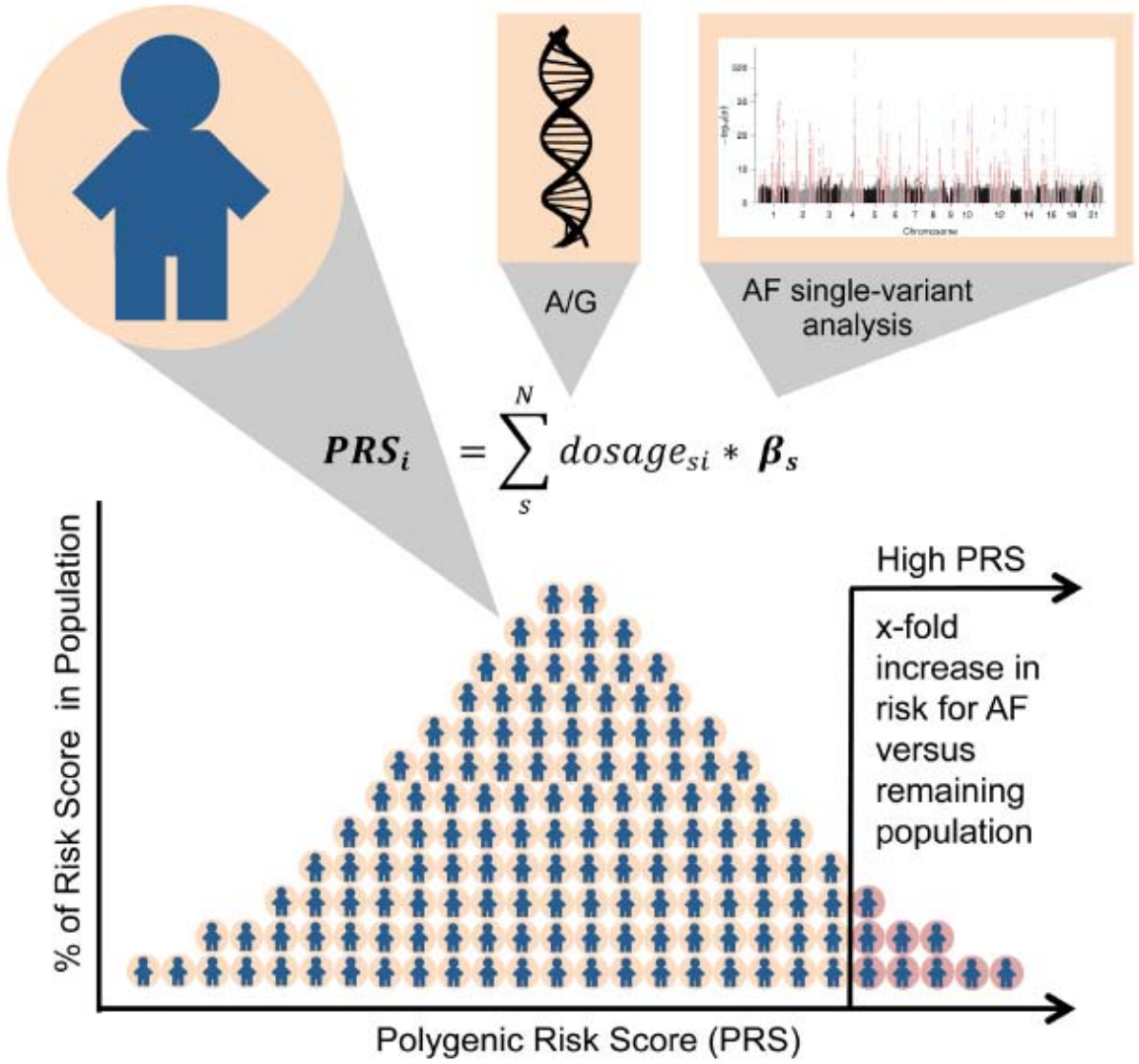
Choi SH et al. JAMA 2018;320:2354-2364

Major AF-associated genes and lines of evidence



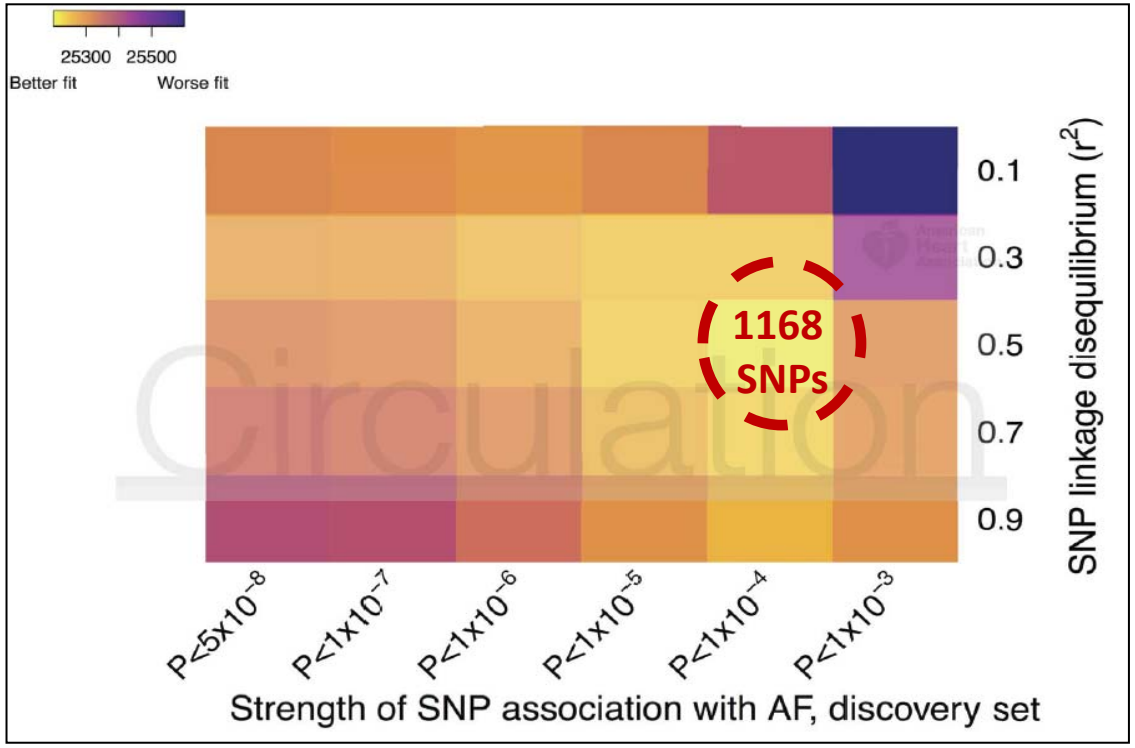
Roselli C et al. Circ Res 2020;127:21-33

Polygenic Risk Scores (PRS) for AF

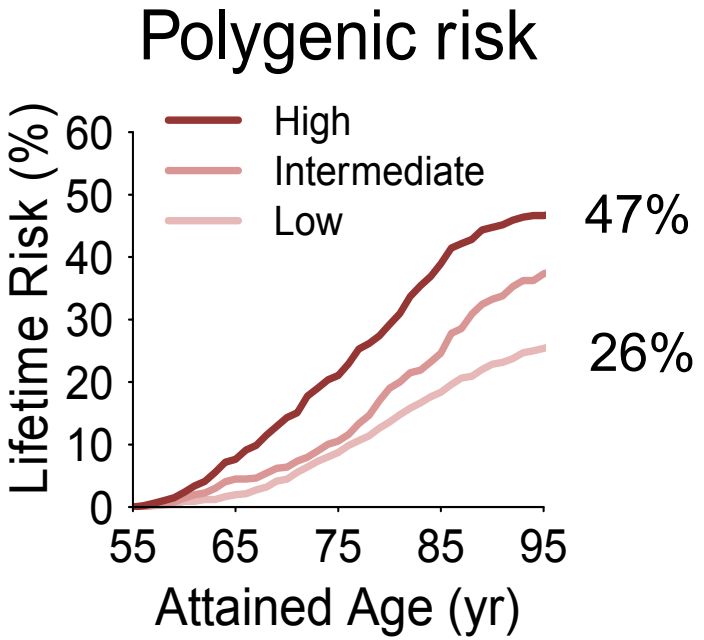


Roselli C et al. Circ Res 2020;127:21-33

A Polygenic Risk Score and Life-time AF risk
: Framingham Heart study (n=5,131) as test set

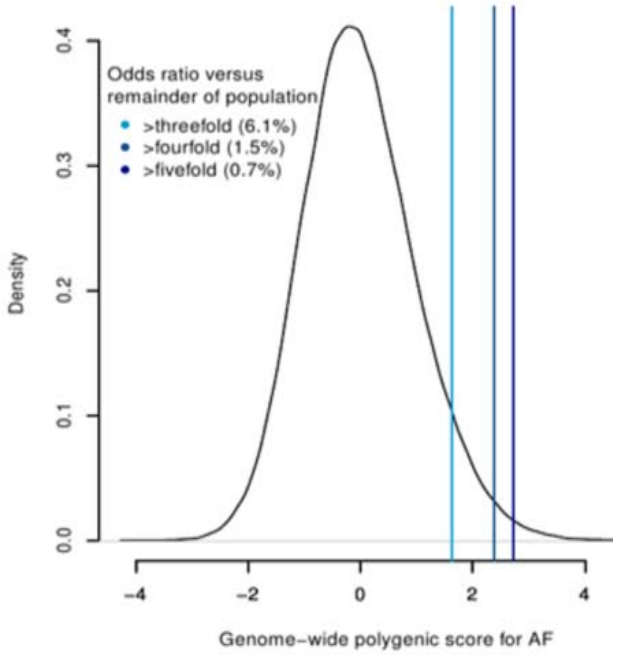


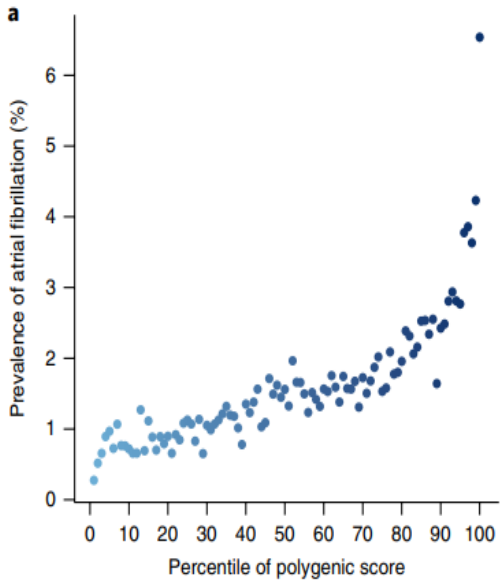
*From UK Biobank

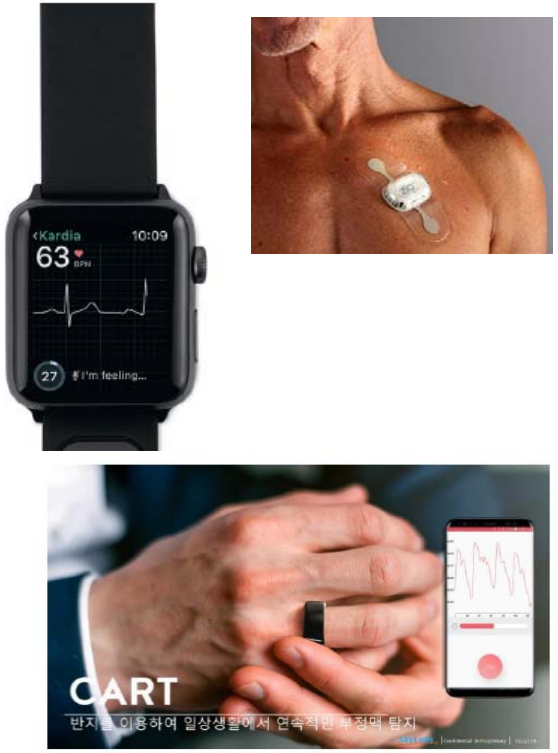


Weng LC et al. Circulation. 2018;137:1027-1038

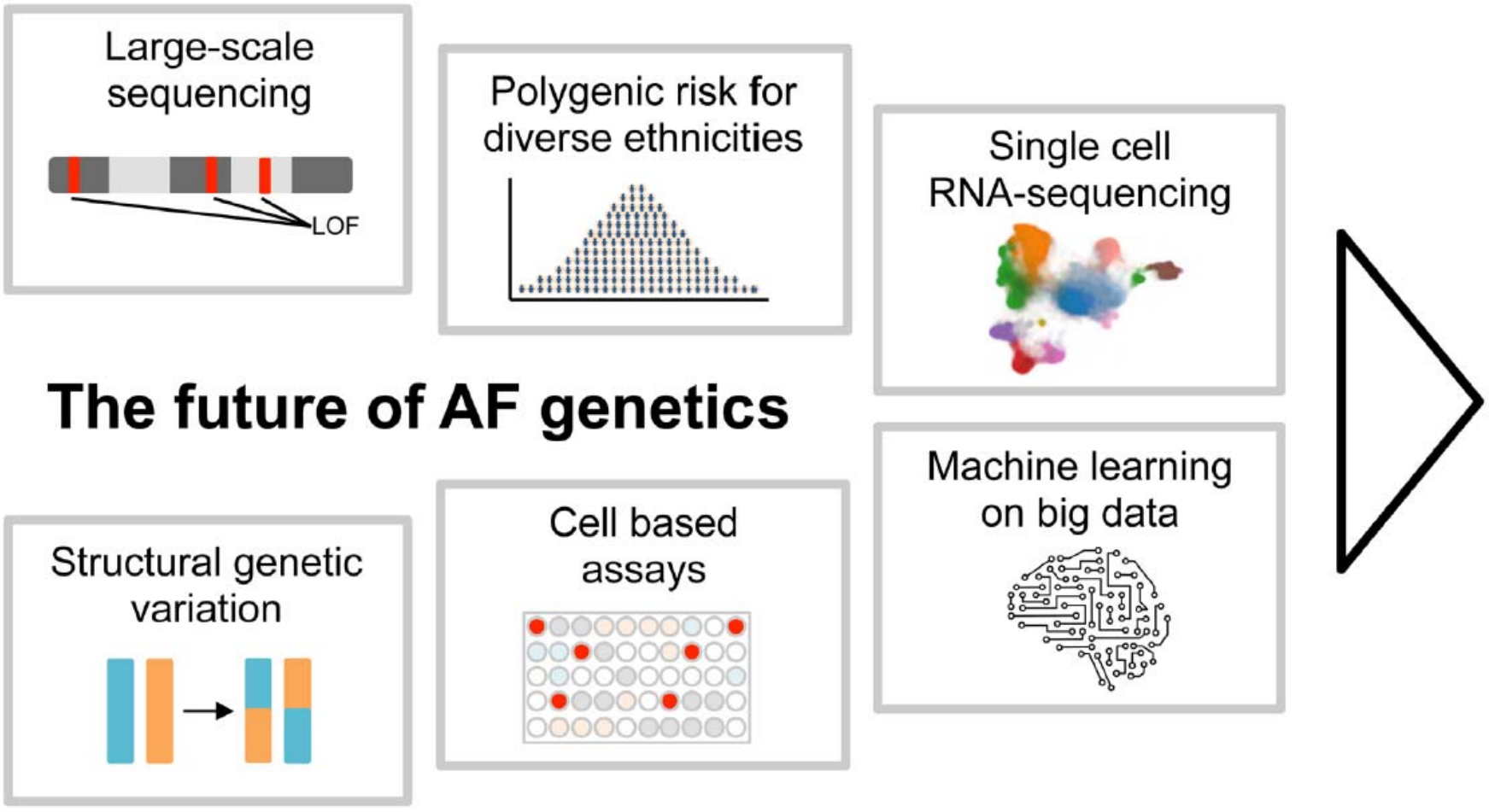
Using AF genetic PRS to detect subclinical AF in high-risk patients







Future directions in AF genetics



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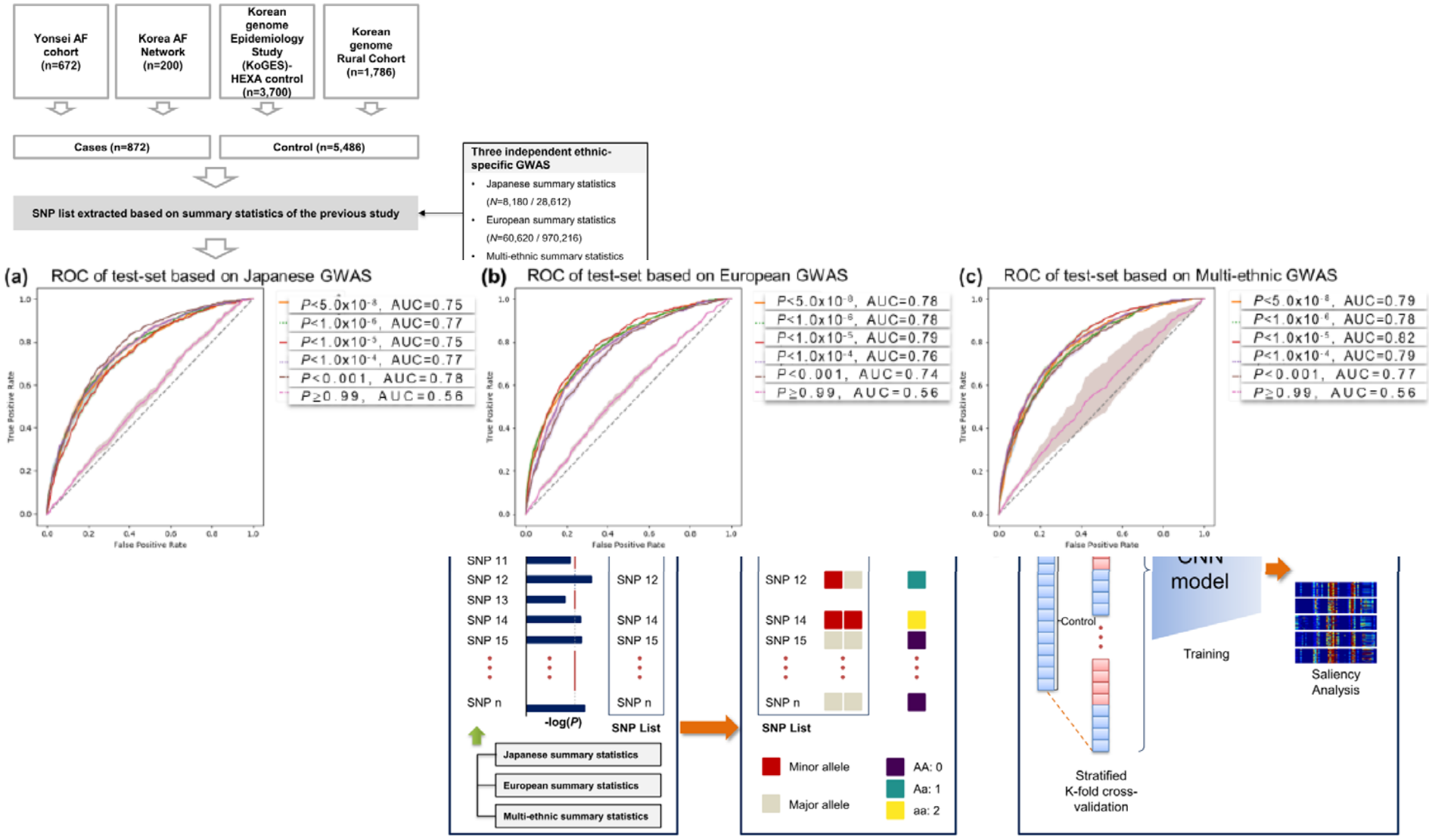
GWAS study-based AI AF prediction?



Kwon OS, Pak HN et al. Under review

Summary

- AF is a complex disease with both environmental and genetic risk factors that contribute to the arrhythmia.
- Rapid progress has been made in identifying many common variant loci in GWAS for AF.
- Recent studies have identified TTN as the gene most commonly associated with mutations in individuals with AF.
- Future directions in AF genetics
  - Structural variation from whole-genome sequencing
  - Expanding gene expression and epigenetic analyses to tissues relevant to AF
  - Developing large-scale functional screens for AF genes
  - Implementing machine learning to identify endophenotypes of AF

Thank you for your attention!

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