

# Meta-analysis of genome-wide associations and polygenic risk prediction for atrial fibrillation in more than 180,000 cases

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## Supplementary Notes

### Supplementary Results

#### Exploratory analysis of low frequency variants

In an exploratory analysis of low frequency variants with MAF < 1% we identified 14 genetic loci (**Figure 1, Supplementary Table 6**). We observed stronger effects (OR range: 1.22 – 4.30) at these low frequency lead variants compared to common lead variants (**Extended Data Figure 1C**). To ensure that low frequency variant associations were not driven by poor genotyping or imputation, we attempted to validate these low frequency variant associations using whole exome sequencing (WES) and whole genome sequencing (WGS) of partially overlapping study cohorts<sup>1</sup>. We could test 11 loci and saw consistent directionality for 10 of them, 5 reached nominal significance (**Supplementary Table 7**). The genetic locus with the largest OR among the rare variants (OR range: 3.01 – 4.30) was close to the genes *NEURL1/SH3PXD2A*. This association was strongest in individuals of East Asian ancestry. Another genetic locus in the Icelandic population on chromosome 11 was tagging the known founder mutation rs397516082 (c.927-2A>G) in the gene *MYPBC3* ( $R^2 > 0.64$ ) that has shown to be associated with hypertrophic cardiomyopathy<sup>2</sup>. As anticipated, there was an inverse correlation between minor allele frequency and AF risk (**Extended Data Figure 1D**).

#### Ancestry specific loci

We then examined the association results for the eight ancestry groups (**Supplementary Tables 2, 4 and 6**). Seven of the common lead variants and three of the low frequency lead variants showed significant heterogeneity of effect estimates by ancestry. A small subset of common lead variants was present in only one of the ancestries. For example, the lead variant rs181513970 was observed in only the FIN ancestry group (closest gene = *POLD1*, OR = 1.44, P-value =  $4.27 \times 10^{-10}$ ), and the variant rs112538624 near *NOL12* was observed in the AdmAFR ancestry group (OR = 2.4, P-value =  $4.47 \times 10^{-08}$ ). Of note, the association at rs112538624 was

only derived from one cohort ( $N_{AF} = 414$ ), and could be a false positive. A replication analysis was not performed due to lack of access to additional samples from this ancestry group.

### Results from MAGMA, PoPS, eQTL, snRNA and coding variation

The region-based method MAGMA (Multi-marker Analysis of GenoMic Annotation) identified 569 genes with  $P$ -value  $< 2.76 \times 10^{-6}$  at AF GWAS loci (**Supplementary Table 8**). The top 3 genes with the lowest MAGMA  $P$ -values were *SH3PXD2A*, *AKAP6* and *ZFHX3*. The similarity-based method PoPs (Polygenic Priority score) incorporates the results from MAGMA and scores genes based on shared annotated traits. **Extended Data Figure 2** shows the distribution of the PoPs-score across all genes and the cutoff based on  $> 3$  standard deviations from the mean that we used to define a high PoPs score. The top 3 genes with the highest PoPs-score were *MYOCD*, *TTN*, and *NKX2-5* (**Supplementary Table 9**).

Next, we sought to integrate the AF GWAS results with single-nuclei and bulk RNA-sequencing transcriptional profiles. First, we evaluated the GWAS results globally leveraging recently emerging single-nuclei transcriptomics data from the healthy human heart<sup>3</sup>. Using LD-score regression we observe the strongest enrichment of AF GWAS heritability near genes upregulated in left atrial cardiomyocytes relative to right atrium, right ventricle, and left ventricle cardiomyocytes (**Extended Data Figure 3A**). Examination of the dedicated cell-types in the left atrial tissue demonstrated that genes expressed in cardiomyocytes were enriched at our AF GWAS loci (**Extended Data Figure 3B** and **Supplementary Table 12**). Second, the sentinel variants were intersected with expression quantitative trait loci (eQTL) from cardiac tissues (GTEx: atrial appendage, left ventricle, MAGNET: left atrium), showing that 142 lead variants were eQTLs (**Supplementary Tables 10** and **11**).

We then investigated the predicted functional consequence of all AF-associated variants located in the protein coding regions of the genome. Four AF variants were predicted to have a high impact via the annotation from the Variant Effect Predictor tool (VEP)<sup>4</sup>, in the genes *RPL3L* (c.1167+1G>A), *PPFIA4* (p.Pro585AlafsTer6), *PTGES3* (c.2\_3insAT) and *GSDMB* (c.662-2A>G) (**Supplementary Table 13**). In *RPL3L*, rs140192228 was predicted to introduce a splice site variant in the gene, a mutation that has previously been reported for AF in a meta-analysis

including deCODE and the UK Biobank<sup>5</sup>. Additional 159 common variants and 6 low frequency missense variants were predicted to have moderate impact on gene function. The largest number of missense variants (N = 25) was found in gene *TTN*, a large structural protein in cardiomyocytes, that has been previously implicated in AF<sup>6,7</sup>. A total of 47 genes harbored a genome-wide significant missense mutation (**Supplementary Table 14**).

### **Comparison of GenePrio and OpenTargets L2G**

Linking causal genes from variants identified in GWAS remains an open challenge in the field. The GenePrio algorithm serves as a heuristic method to prioritize candidate genes based on five lines of evidence. It was not benchmarked against gold standard sets of genes (as gold standards are not straightforward to derive). We also note that GenePrio already incorporates many data sources used in other strategies of prioritization, including a complete prioritization algorithm in and of itself (the Polygenic Priority Score (PoPS)). Nonetheless, we sought to compare the selection of genes from GenePrio to another contemporary approach, namely OpenTargets locus to gene (L2G) model. The OpenTargets L2G model uses features such as variant pathogenicity, colocalization of molecular QTLs, gene distance from credible set variants, and chromatin interactions. GenePrio uses similar features to this method, but unlike the OpenTargets L2G model, GenePrio focuses specifically on the most relevant tissues for eQTLs and cell type specific expression based on *a priori* knowledge of the disease.

To compare GenePrio to the OpenTargets L2G prioritization model, we extracted the L2G results from OpenTargets for the GWAS from Roselli et al., 2018 as these results are provided with open access by OpenTargets. We then applied our GenePrio approach to these GWAS results and compared the two gene prioritization strategies. In total, 101 loci are included in the OpenTargets L2G model from this GWAS, and of these, OpenTargets L2G prioritizes one or more genes at 77 (76.2%) loci. Conversely, GenePrio only prioritized genes at 52 (51.4%) loci, a notably more conservative approach. Notably, 42 of the 101 loci have at least one gene prioritized in both methods, of which 36 (85.7%) have the same gene prioritized, suggesting

these methods converge to similar prioritization results. The specific breakdown of loci are as follows:

**Prioritized only by GenePrio (n=10):**

*XPO1, REEP1, ACVR2A, TTN, FAM13B, ATXN1, GPR22, NACA, RPL3L, CHRNA1*

**Prioritized only by OpenTargets L2G (n=35):**

*GJA5, NUCKS1, KIF3C, MXD1, CAND2, THRB, EPHA3, PHLDB2, GNB4, ARHGAP10, KDM1B, SMIM29, SUN1, DGKB, CREB5, (MTSS1, ZNF572, SQLE)\*, ZFAT, PTK2, MLLT3, APOE, ZNF462, LRMDA, NEURL1, SORL1, SOX5, TBX3, (ESR2, SYNE2)\*, IRF2BPL, TLE3, HCN4, ARNT2, KCNJ2, SMAD7, GATA5, CLIC6*

**Prioritized concordantly by both OpenTargets L2G and GenePrio (n=36):**

*CASZ1, KCND3, CASQ2, METTL11B, PRRX1, PPFIA4, CEP68, WIPF1, SPATS2L, WDR1, PITX2, CAMK2D, HAND2, KCNN2, NR3C1, NKX2-5, CDKN1A, EYA4, CAV1, KCNH2, ASAH1, FBXO32, PSMB7, SYNPO2L, KCNJ5, SSPN, PKP2, BEST3, TBX5, CCDC92, AKAP6, CFL2, IGF1R, ZFHX3, MYOCD, MAPT*

**Prioritized discordantly by OpenTargets L2G and GenePrio (n=6, formatted as**

**GenePrio:OpenTargets L2G):**

*SCN5A:SCN10A, SLC25A26:LRIG1, UBE2D3:SLC9B1, PLN:SLC35F1, GTF2IRD2:GTF2I, MYH6:MYH7*

\*Note: Multiple genes prioritized by OpenTargets L2G at these loci.

## Study descriptions

The following studies have previously been described: ARIC<sup>8</sup>, BBJ<sup>9</sup>, deCODE<sup>10</sup>, DiscovEHR<sup>10</sup>, FHS<sup>8</sup>, HUNT<sup>10</sup>, KAFN<sup>11</sup>, MESA<sup>6</sup>, MGI<sup>10</sup>, MGH CAMP<sup>6</sup>, PHB<sup>12</sup>, SiGN<sup>13</sup>, SPHFC<sup>6</sup>, UKBB<sup>14</sup> and WGHS<sup>8</sup>.

**GAPP, BEAT-AF and Swiss-AF Cohorts (GAPPBEATSWISS):** The study Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors (GAPP) is population based, including inhabitants of the Principality of Liechtenstein between the ages of 25 to 41<sup>15</sup>. Participants free of AF from the GAPP study were used as controls in this analysis.

The Basel atrial fibrillation cohort (BEAT-AF) study is a prospective study among patients with AF across multiple centers. Swiss-AF is a prospective multicenter cohort study in Switzerland including AF patients > 65 years.

**Broad CardioVascular Disease initiative study (Broad CVDi Study):** The Broad CVDi study is an extension of the Broad AF study. It is a multi-study case control collection at the Broad institute focused on cardiovascular diseases including atrial fibrillation, mitral valve prolapse, Atrioventricular nodal reentrant tachycardia (AVNRT), Supraventricular tachycardia (SVT) and Bradyarrhythmia. The DNA for each sample was imported to the Broad and jointly genotyped on the Infinium PsychArray-24 v1.2 array. The genotyping approach, QC and imputation have previously been described<sup>12</sup>. Over 35,000 participants were contributed to this collection with an average case control mix of 2:1. Participants that were collected as cases for cardiac traits or diseases other than AF were excluded for this analysis. 91% of the participants in the Broad CVDi study were of European ancestry, 3% of African American ancestry, 2% from Brazil. Individual studies contributing to this AF case control analysis were: AFCT, AFLMU, Australian Familial AF Study, BioVU, CVBio, Duke, EAST AFNET4, GENAF, German Heart Center Controls, GerMIFS, GGAF, Hopkins, HVH, Intermountain, MGH AF, MGH DOFEGEN, MGH MVP, MGH Stroke, MPP AF, MPP Echo, Penn, PHB, TCAI, UCSF, UMass and VAFAR. These studies have previously been described<sup>12</sup>.

### **The Copenhagen Hospital Biobank Cardiovascular Study and the Danish Blood Donor Study**

**(CHB-CVS DBDS):** This study is part of the study: "Genetics of cardiovascular disease" – a genome-wide association study on repository samples from CHB - the CHB-CVS study. CHB has previously been described<sup>16</sup>. CHB-CVS is a genetic study on patients from CHB with cardiovascular diseases identified through the Danish National Patient Registry (NPR). CHB-CVS is approved by the National Committee on Health Research Ethics (NVC 1708829) and the Danish Data Protection Agency (P-2019-93). DBDS is a prospective cohort and biobank study on general health among blood donors. DBDS has been genotyped by deCODE Genetics<sup>17</sup>. The current work includes 659 cases with AF and 36,475 healthy controls. Phenotypes were identified through NPR. The genetic studies within DBDS is approved by the National Committee on Health Research Ethics (NVC 1700407) and the Data Protection Agency (P-2019-99).

**ENGAGE AF-TIMI 48 (TIMI 48):** TIMI 48 was a 3-arm randomized, double-blind, double-dummy trial of 21,105 participants<sup>18</sup>. The trial compares two doses of edoxaban to placebo. Enrollment criteria were presence of atrial fibrillation requiring anticoagulation. Participants of the trial had the following comorbidities, diabetes (38%), stroke/TIA (28%), and congestive heart failure (57%). Phenotypes were adjudicated by physicians based on patient interview and medical record/imaging review.

**FinnGen:** FinnGen is a public-private partnership across Finnish universities, hospitals, biobanks and pharmaceutical companies. It aims at completing genotyping for genome-wide association studies for all included samples, and utilizes extensive registry data that is available on all Finns<sup>19</sup>. This study includes results from the release R4, that was released to the public in Q4 2020 and includes 176,899 samples (<https://finngen.gitbook.io/documentation/v/r4/>).

**FOURIER (TIMI 59):** Was a multinational, randomized, double-blind, placebo-controlled trial of 27,564 participants<sup>20</sup>. The trial compared the PCSK9 inhibitor evolocumab in patients with myocardial infarction, stroke, or peripheral artery disease (PAD). Participants of the trial had the

following comorbidities, hypertension (80%), diabetes (37%), and prior myocardial infarction (81%). Phenotypes were adjudicated by physicians based on patient interview and medical record/imaging review.

**The Health and Retirement Study (HRS):** The HRS study<sup>21</sup> is a longitudinal survey of a representative sample of Americans over the age of 50. The current sample is over 26,000 persons in 17,000 households. The study interviews respondents every two years about income and wealth, health and use of health services, work and retirement, and family connections. DNA was extracted from saliva collected during a face-to-face interview in the respondents' homes. These data represent respondents who provided DNA samples and signed consent forms in 2006, 2008, 2010, and 2012. Prevalent AF at time of DNA draw as determined by Medicare Claims (Medicare linkage and three years of Part A&B FFS coverage immediately prior to DNA draw). Cases: requires 1 IP claim or 2 OP/PB claims in 1-year period. Controls: no AF in claims prior to DNA draw.

**PEGASUS (TIMI 54):** Was a multinational, randomized, double-blind, placebo-controlled trial of 21,162 participants<sup>22</sup>. It studied the efficacy of ticagrelor in stable ischemic heart disease. Participants in the trial presented with prior myocardial infarction. Participants of the trial had the following comorbidities, smoking (17%), hypertension (78%), diabetes (32%), prior PCI (83%), and prior CABG (60%). Phenotypes were adjudicated by physicians based on patient interview and medical record/imaging review.

**SAVOR (TIMI 53):** Was a multinational, randomized, double-blind, placebo-controlled trial of 16,492 participants<sup>23</sup>. Saxagliptin was randomized to placebo in diabetics. Participants of the trial had the following comorbidities, atherosclerosis (78%), HTN (81%), and heart failure (13%). Phenotypes were adjudicated by physicians based on patient interview and medical record/imaging review.



**SOLID (TIMI 52):** Was a multinational, randomized, double-blind, placebo-controlled trial of 13 026 participants, that randomized darapladib<sup>24</sup>. Darapladib was a selective inhibitor of Lp-PLA2 enzyme in patients within 30 days of acute coronary syndrome. The acute coronary syndrome events were ST-elevation myocardial infarction (45% of patients), non–ST-elevation myocardial infarction (43% of patients), and unstable angina (12% of patients). Participants of the trial had the following comorbidities, hypertension (73%), diabetes (35%), and prior MI (31%). Phenotypes were adjudicated by physicians based on patient interview and medical record/imaging review.

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