Electrical Phenotypes of Genetic Risk for Atrial Fibrillation

Proposal for Validation Cohort

AF is a multifactorial disease that is both highly prevalent and burdensome, with a lifetime incidence of 1 out of 3-4 individuals. Although We have a limited understanding of the clinical factors that lead to atrial fibrillation (**AF**) pathogenesis, there is growing evidence of the genetic underpinnings of AF (Weng et al. 2020; Choi et al. 2020). It is clear that AF maintenance and pro-generation are a property of the atrial substrate, which can likely be further phenotyped based on how the atria are remodeled. The relationship of the atrial substrate to underlying genetic factors has somewhat been seen in studies evaluating electrocardiogram (ECG) associations with genetic variants (Verweij et al. 2020; Weng et al. 2020; Holmqvist et al. 2015; Husser et al. 2009; Choi et al. 2021). In this proposal, I plan to correlate the genetic manifestations of AF with the electrical properties of through electrocardiographic (**ECG**) evaluation of atrial and ventricular depolarization and repolarization using a deep neural network (**DNN**).

Relevant work previously is primarily by Verweij et al. (2020) and van de Leur et al. (2021), who have evaluated ECG relationships with genetic variants. Verweij et al. (2020) noted that specific temporal features of the ECG could be associated with genetic abnormalities ([Figure 1](#fig-ecg-variants)). van de Leur et al. (2021) expanded on this to understand the electrical phenotype of a specific disease, in this case, phosphalamban cardiomyopathy, and demonstrated that a neural network could help identify morphological features of the ECG that were associated with the disease, best seen in [Figure 2](#fig-ecg-dnn). Our proposal varies from the previous work as the goal is instead to evaluate the potential mechanisms of AF, instead of novel diagnosis of specific genetic variants. By comparing ECG of individuals with known AF into specific endotypes based on genetic variants associated with their AF, we can understand how variants may lead to AF through electrophyioslogical manifestations. As such, I have characterized genes putatively associated with cardiovascular disease into 4 categories:

1. Structural genes (e.g. TTN, PITX2, LMNA, NUP155, GJA1/5)
2. Ion channel genes (e.g. KCNE1-5, KCNQ1, SCN5A), subdivided by current
3. Metabolic genes
4. Inflammatory genes

These categories, from a causal perspective, share mechanistic similarities in how they may lead to AF. To identify if electrophysiological manifestations exist, in a sample with documented paroxysmal AF, individuals that carry a loss-of-function (**LOF**) in one of the above gene categories, or they may be *wild-type* (no known deleterious AF-associated genes).

We have completed a feasibility study using the *TTN* gene as a proof-of-concept, seen in [Figure 3](#fig-shah-ttn), using a convolutional neural network with bidirectional memory. The model was trained on a cohort of n=200 individuals with known paroxysmal AF, with n=100 being reserved as a testing data set. Of those, using the strictest variant effect prediction definition for LOF, n=4 individuals were considered as cases (roughly 2% of the cohort). Each individual contributed 1 to 10 ECG, with each ECG being segmented into individual sinus beats, and each sinus beat used as a training (or test) data array. We had a sensitivity and specificity of 98% and 95%, with a balanced accuracy of 96% and detection prevalence of 95%.

I aim to expand this project to better understand the electrocardiographyic phenotype of AF, to better understand mechanisms behind AF pathogenesis, and identify individuals at different degrees of risk for AF. My aims are as follow:

1. **Monogenic Aim**: Validate a DNN model to identify deleterious gene variants associated with AF in individuals with known AF, with cases defined as those with: a) sarcomeric or structural proteins, b) ion channel-related proteins, c) metabolic proteins, and d) inflammatory proteins that have a known association with cardiovascular disease.
2. **Polygenic Aim**: Train a DNN model to assess the polygenic risk (PGS) of AF in individuals with known AF and dense SNP genotyping data, based on recent, validated AF-GWAS polygenic risk scores (Khera et al. 2018; Marston et al. 2023). The model would be trained to predict the percent PGS of AF, however the input is a 12-lead ECG.

I utilized participants from the UIC Multi-Ethnic AF Registry as the primary study population, who have a combination of WES and dense SNP genotyping data. This allowed me to generate a small DNN model for both monogenic and polygenic patterns. However, the sample size was small, reducing generalizability. I propose to utilize a large, external cohort, such the UK Biobank (n=68,091 with complete data), as well as additional populations such as the ARIC cohorts, the US-CHARGE participating studies, and/or the Cardiac Heart Study. The All of Us study is limited to only 30% of the population with ECG tracings. I propose testing (and/or additional training) on these large cohorts to validate the model for monogenic and polygenic ECG-phenotypes of AF. My approach is the next logical step in better understanding the relationship between genetic variants and AF risk over time, and helps to create an *ECG-informed risk assessment* for the phenotypes of AF.

|  |
| --- |
| Figure 1: Verweij et al. (2020) |

|  |
| --- |
| Figure 2: van de Leur et al. (2021) |

|  |
| --- |
| Figure 3: *Shah 2024 (in progress)* |

Choi, Seung Hoan, Sean J. Jurgens, Christopher M. Haggerty, Amelia W. Hall, Jennifer L. Halford, Valerie N. Morrill, Lu-Chen Weng, et al. 2021. “Rare Coding Variants Associated With Electrocardiographic Intervals Identify Monogenic Arrhythmia Susceptibility Genes.” *Circulation. Genomic and Precision Medicine* 14 (4): e003300. <https://doi.org/10.1161/CIRCGEN.120.003300>.

Choi, Seung Hoan, Sean J. Jurgens, Lu-Chen Weng, James P. Pirruccello, Carolina Roselli, Mark Chaffin, Christina J.-Y. Lee, et al. 2020. “Monogenic and Polygenic Contributions to Atrial Fibrillation Risk.” *Circulation Research* 126 (2): 200–209. <https://doi.org/10.1161/CIRCRESAHA.119.315686>.

Holmqvist, Fredrik, Sunghee Kim, Benjamin A. Steinberg, James A. Reiffel, Kenneth W. Mahaffey, Bernard J. Gersh, Gregg C. Fonarow, et al. 2015. “Heart Rate Is Associated with Progression of Atrial Fibrillation, Independent of Rhythm.” *Heart (British Cardiac Society)* 101 (11): 894–99. <https://doi.org/10.1136/heartjnl-2014-307043>.

Husser, Daniela, Martin Stridh, Leif Sörnmo, Dan M. Roden, Dawood Darbar, and Andreas Bollmann. 2009. “A Genotype-Dependent Intermediate ECG Phenotype in Patients With Persistent Lone Atrial Fibrillation.” *Circulation: Arrhythmia and Electrophysiology* 2 (1): 24–28. <https://doi.org/10.1161/CIRCEP.108.799098>.

Khera, Amit V., Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan, et al. 2018. “Genome-Wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations.” *Nature Genetics* 50 (9, 9): 1219–24. <https://doi.org/10.1038/s41588-018-0183-z>.

Leur, Rutger R. van de, Karim Taha, Max N. Bos, Jeroen F. van der Heijden, Deepak Gupta, Maarten J. Cramer, Rutger J. Hassink, et al. 2021. “Discovering and Visualizing Disease-Specific Electrocardiogram Features Using Deep Learning.” *Circulation: Arrhythmia and Electrophysiology* 14 (2): e009056. <https://doi.org/10.1161/CIRCEP.120.009056>.

Marston, Nicholas A, Amanda C Garfinkel, Frederick K Kamanu, Giorgio M Melloni, Carolina Roselli, Petr Jarolim, David D Berg, et al. 2023. “A Polygenic Risk Score Predicts Atrial Fibrillation in Cardiovascular Disease.” *European Heart Journal* 44 (3): 221–31. <https://doi.org/10.1093/eurheartj/ehac460>.

Verweij, Niek, Jan-Walter Benjamins, Michael P. Morley, Yordi J. Van De Vegte, Alexander Teumer, Teresa Trenkwalder, Wibke Reinhard, Thomas P. Cappola, and Pim Van Der Harst. 2020. “The Genetic Makeup of the Electrocardiogram.” *Cell Systems* 11 (3): 229–238.e5. <https://doi.org/10.1016/j.cels.2020.08.005>.

Weng, Lu-Chen, Amelia Weber Hall, Seung Hoan Choi, Sean J. Jurgens, Jeffrey Haessler, Nathan A. Bihlmeyer, Niels Grarup, et al. 2020. “Genetic Determinants of Electrocardiographic P-Wave Duration and Relation to Atrial Fibrillation.” *Circulation. Genomic and Precision Medicine* 13 (5): 387–95. <https://doi.org/10.1161/CIRCGEN.119.002874>.