**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT356 |
| **Submission Date** | 8/20/2019 |
| **Project Title** | The Association between Variants in Ion Channel Genes and Arrhythmia Phenotypes |
| **Tentative Lead Investigator (first author)** | Ben Shoemaker |
| **Tentative Senior Authors (last author)** | Dan Roden |
| **All other authors**  | Andrew Glazer, Brett Kroncke, Christian Shaffer, Yuko Wada, Giovanni Davogustto, Quinn Wells, Jonathan Mosley, Zachary Yoneda, Josh Denny and “The eMERGE Network” plus ***any additional eMERGE authors interested in participating*** |
| **Sites Involved** | A network-wide study (all sites invited to participate).  |
| **Background / Significance** | Genetic testing for rare variants associated with inherited arrhythmia syndromes (i.e. Long QT Syndrome, Brugada Syndrome, etc.) is becoming increasingly common in clinical practice, as is the incidental detection of these variants during research or commercial sequencing. We seek to define the relationship between pathogenic, likely pathogenic, and variants of undetermined significance) in *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNJ2, RYR2, or CACNA1C* and code-based arrhythmia phenotypes.  |
| **Outline of Project** | 1. Variants are designated pathogenic, likely pathogenic or variants of uncertain significance by the eMERGE-3 sequencing centers and annotation WG.
2. Arrhythmia phenotypes will be derived from the core phenotype dataset, using diagnosis and procedure codes. These will be aggregated into the following groups: 1) Atrail Fibrillation (atrial fibrillation, atrial flutter), 2) Ventricular Arrhythmia (ventricular tachycardia, ventricular fibrillation, premature ventricular contractions, ICD implant) 3) Conduction System Disease (sick sinus syndrome, high grade atrioventricular block, bradycardia- not otherwise specified, left bundle branch block, or right bundle branch block, pacemaker). 4) syncope
3. The primary analysis will test for an association between P, LP, and VUS variants at the individual gene level and the arrhythmia phenotypes. Multivariable adjustment will be made for age, sex, and principal components of ancestry.
4. Secondary analyses will test for associations between arrhythmia phenotypes and 1) the pathogenicity subgroups (pathogenic, likely pathogenic, or VUS), 2) variation restricted to specific gene regions known to more strongly affect protein structure/function (e.g. amino acids 44-466, 2246-2534, 3778-4201, 4497-4959 in RyR2). Associations will be examined for P,LP, or VUS occurring more than once in the dataset, and for associations of individual components (atrial fibrillation, ventricular arrhythmia, conduction system disease, syncope) and variants.
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| **Desired****Variables (essential for analysis****indicated by \*)** | * Core data set
* eMERGE-seq panel data for *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNJ2, RYR2, or CACNA1C*
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| **Desired data** | * Core data set
* eMERGE-seq panel data for *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNJ2, RYR2, or CACNA1C*
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| **Planned Statistical Analyses** |  1. Descriptive statistics for the frequency of arrhythmia phenotypes between ultra-rare variant carriers and non-carriers reported for each specific ion channel gene.
2. Multivariable logistic regression tests the association between each arrhythmia phenotype (yes/no) as the outcome and the primary determinant of ultra-rare variant status (yes/no) for a given ion channel gene. Each gene will be run in a separate regression model. Adjustment will be made for age at enrollment, sex, and principal components of ancestry.
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| **Ethical considerations** | There are no additional risks involved. The data will be stored at a secured location in the data storage system of Dr. Dan Roden at Vanderbilt. No data will be shared with unauthorized third parties. Patient identity will not be compromised by the proposed analysis. We will also abide by the EMERGE guidelines in this regard. |
| **Target Journal** | TBD, depending on the findings |
| **Milestones\*\*** | Total Duration of the study: 6 months |