**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT 355 |
| **Submission Date** | 8/27/2019 |
| **Project Title** | The Association between Variants in Long QT Syndrome Susceptibility Genes and ECG features.  |
| **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 such as the Long QT Syndrome is becoming increasingly common in clinical practice, as is the incidental detection of these variants during research or commercial sequencing. (1) We seek to define the effect of pathogenic, likely pathogenic, and variants of undetermined significance in *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNJ2, or CACNA1C* on the QT interval. (2) We seek to define the effect of pathogenic, likely pathogenic, and variants of undetermined significance in *SCN5A* on the Brugada Syndrome ECG phenotype.  |
| **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. QTc data are generated using an algorithm that selects ECGs appropriate for QT interpretation. The algorithm has been developed at Vanderbilt and validated at Mayo. These ECGs meet criteria that exclude potential confounders such as QT prolonging medicines, electrolyte disturbances, or tachycardia/bradycardia/conduction disease. The QTc value for the first qualifying ECG will be used for analysis. The same criteria will be used to select ECGs for the Brugada Syndrome analysis.
3. For the QTc analysis, ECG data from variant carriers only will be sufficient to perform the analysis below, since population controls are well-established. For the Brugada syndrome analysis, copies of ECGs stripped of identifiers and coded by each site will be read blind to case-control status by 2 investigators at Vanderbilt, with a 3rd acting as tie-breaker if there is no agreement. For this analysis, ECGs from variant carriers and age-, sex-, and ancestry matched non-carriers will be required from participating sites.
4. The primary QTc analysis will determine the proportion of variant carriers with QTc values > accepted cutoffs (470 for males, 480 for females) and >500. The primary BrS analysis will determine the number proportion of *SCN5A* variant carriers with/without the type 1, 2, and 3 BrS ECG patterns compared to that in controls.
5. Secondary analyses will determine these proportions by individual variant and by individual gene.

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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, or CACNA1C*
* QTc intervals
* ECG tracings
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| **Desired data** | * Core data set
* eMERGE-seq panel data for *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNJ2, RYR2, or CACNA1C*
* *QTc* intervals
* ECG tracings
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| **Planned Statistical Analyses** |  1. Descriptive statistics for the median and IQR for the QTc interval between ultra-rare variant carriers and non-carriers reported for each specific ion channel gene.
2. Multivariable linear regression tests the association between the QTc interval (continuous) 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 |