**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT248 |
| **Submission Date** | 8/16/2017 |
| **Project Title** | Association Studies of Variants *in KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, and *KCNE1* with arrhythmia and ECG phenotypes in 25,000 eMERGE 3 participants |
| **Tentative Lead Investigator (first author)** | Ben Shoemaker |
| **Tentative Senior Authors (last author)** | Dan Roden |
| **All other authors**  | Quinn Wells, Jonathan Mosley, Zachary Yoneda, Josh Denny, Andrew Glazer, Brett Kroncke 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 association between variants in arrhythmia-associated genes with inherited arrhythmia syndromes and ECG phenotypes. We will test the hypotheses that: 1. the presence of a likely pathogenic or pathogenic rare variant in *KCNQ1, KCNH2, ANK2, CACNA1C, KCNE1*, or *SCN5A* will be associated with prolongation of the QT interval
2. the presence of a likely pathogenic or pathogenic rare variant in *SCN5A* will be associated with prolongation of the PR and/or QRS intervals, or “Brugada Syndrome” in the ECG impressions.
3. the presence of a likely pathogenic or pathogenic rare variant in *RYR2* will be associated with prolongation of the RR interval
4. the presence of a variant of undetermined significance in *KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, or *KCNE1* is associated with a change in the corresponding ECG trait.
5. there is a combined effect on quantitative ECG traits conferred by rare variants and also common variants. The effect of common variants can partially be assessed using a polygenic risk score derived from SNPs previously found to be associated with the given ECG trait, and assessed on the eMERGE-Seq platform
6. the presence of common variants modulate the penetrance of rare variants for development of inherited arrhythmia syndromes. The effect of common variants can partially be assessed using SNPs on the eMERGE-Seq platform
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| **Outline of Project** | 1. Determine the frequency of pathogenic/likely pathogenic variants in *KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, and *KCNE1* among participants in eMERGE 3.
2. Determine the association of pathogenic/likely pathogenic variants in *KCNQ1, KCNH2, RyR2, SCN5A, ANK2, CACNA1C*, and *KCNE1* on ECG traits
3. Determine the combined effect of pathogenic/likely pathogenic rare variants in *KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, and *KCNE1,* and a common variant polygenic risk score on ECG traits derived from prior GWAS studies for SNPs included on the EmergeSeq panel
4. Determine the penetrance of inherited arrhythmia syndromes (i.e. Long QT Syndrome, Brugada Syndrome, etc) in carriers of pathogenic/likely pathogenic variants in *KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, and *KCNE1*
5. Determine the combined effect of pathogenic/likely pathogenic rare variants in *KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, and *KCNE1,* and a common variant polygenic risk score derived from prior GWAS studies for SNPs included on the EmergeSeq panel on development of inherited arrhythmia syndromes.
6. Determine the association between the presence of a variant of undetermined significance in *KCNQ1, KCNH2, RYR2, SCN5A, ANK2, CACNA1C*, or *KCNE1* and a change in the corresponding ECG trait.
7. Manuscript preparation and submission.
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| **Desired****Variables (essential for analysis****indicated by \*)** | * Copies of electrocardiograms for morphology assessment (i.e. for Brugada pattern)
* Copies of records from specialty provider referral (as part of e3)
* Quantitative ECG intervals (RR, PR, QRS, QT,)
* List of selected medications (QT prolonging, AVN blocking, etc.)
* Atrial fibrillation phenotype (developed by Vanderbilt)
* Age, sex, race/ethnicity\*
* PheWAS codes
* ICD9 and ICD10 codes
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| **Desired data** | * *KCNQ1, KCNH2, RyR2, SCN5A, ANK2, CACNA1C*, and *KCNE1* sequence data in E3 participants (EMERGE-seq panel data)
* Sequence data for ECG and arrhythmia risk SNPs typed on EMERGE-seq
* PheWAS and ICD9/10 codes
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| **Planned Statistical Analyses** |  1. Identification of rare coding variants in *KCNQ1, KCNH2, RyR2, SCN5A, ANK2, CACNA1C*, and *KCNE1*
2. Rare variant burden tests to detect associations with phenotypes
3. Common ECG trait risk allele analyses in association with the phenotype, including genetic risk score analyses and tests of effect modification for the rare variants detected above.
4. PheWAS of rare variants in *KCNQ1, KCNH2, RyR2, SCN5A, ANK2, CACNA1C*, and *KCNE1* in among E3 sequenced participants
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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: 2 years |