**eMERGE Network Proposal for Analysis**

Manuscript Concept Sheet

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| **Reference Number** | NT243 |
| **Submission Date** | 7/5/2017 |
| **Project Title** | A comparison of genetic effects for Migraine in children versus adults using eMERGE participants. |
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| **All other authors** | Todd Lingren, Beth Cobb, John Harley, |
| **Sites Involved** | All eMERGE sites |
| **Background / Significance** | Migraine ranks among the 20 most disabling diseases and has been estimated as the most costly neurological disorder, with a considerable impact on public health. Genetic factors have been shown to play an important role in the pathogenesis of migraine. In contrast to the rare familial hemiplegic migraine (FHM), which is dominantly inherited with at least four different genetic subtypes, migraine without aura (MO) and migraine with typical aura (MA) have complex inheritance. Migraine occurs at all ages and may even begin in infancy as represented by intermittent colic. In fact, according to The International Classification of Headache Disorders 3rd edition (ICHD-3) certain features of migraine in children may differ from typical features in adults for example it is often bilateral in children, and unilateral pain usually emerges in late adolescence or early adulthood. According to GWAS-catalog, there are 16 migraines genetic studies with 82 associations at the level of genome wide significance but almost all of them consist only of adult population. Given the wide spectrum of population in eMERGE, in this study we a) explore current understanding of migraine genetics, moving from syndromic and monogenic forms to oligogenic/polygenic migraines through genome-wide association studies, b) compare the effects between adult and pediatric as well as clinical subtypes of migraine, including migraine with aura, without aura c) PheWAS study on some well-established monogenic and polygenic effects for this trait including CACNA1A (FHM1), ATP1A2 (FHM2), and SCN1A (FHM3) as well as MTHFR, TGFBR2 MTDH, LRP1, PRDM16, MEF2D, ASTN2, and PHACTR1. |
| **Outline of Project** | 1. Validation of already developed pediatric algorithm for Migraine in adult cohorts by rule-based method and ICD codes. 2. Genotyping local pediatric patients with Migraine, to increase the pediatric sample size 3. Implementing the algorithm across network and identifying cases and controls 4. Perform GWAS study on adult and pediatric cohort separately and explore /compare the results   Also perform PheWAS on well-established known effects as listed above. |
| **Desired**  **Variables (essential for analysis**  **indicated by \*)** | 1. Demographic, ICD-9, gender, age of first diagnosis 2. Migraine sub-type, Exclusion criteria (ICD-9-10) and Comorbidities according to data dictionary (DD) 3. Genetic-data: both whole genome imputation- final version, and emerge-sequencing data will be evaluated |
| **Planned Statistical Analyses** | 1. Logistic regression GWAS, gene-based and pathway enrichment analysis as well as test for pleiotropy in Phewas approach |
| **Ethical considerations** | 1. None. |
| **Target Journal** | TBD |
| **Milestones\*\*** | 1. 12/2017 : adapting pediatric algorithm for adult cohorts and secondary validation 2. 3/2018: implementing at all participating sites 3. 6/30/2018: 1st draft sent   8/31/2018: submit to journal |
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