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| **eMERGE Network: Proposal for Analysis**  Project/Manuscript Concept Sheet | |
| **Reference Number** | NT275 |
| **Submission Date** | March 21, 2018 |
| **Project Title** | New Genetic Loci for Obstructive Sleep Apnea |
| **Tentative Lead Investigator** *(first author)* | Sarah Pendergrass, Geisinger (spendergrass@geisinger.edu) |
| **Tentative Senior Author**  *(last author)* | Olivia Veatch, Vanderbilt University and University of Pennsylvania |
| **All Other Authors** | Les Kirchner, Geisinger ([hlkirchner@geisinger.edu](mailto:hlkirchner@geisinger.edu))  Christopher Bauer, Geisinger  Navya Josyula, Geisinger  Ken Borthwick, Geisinger  Marc Williams, Geisinger  Allan Pack, UPenn  Brendan T. Keenan, UPenn  Diego R. Mazzotti, UPenn  Beth A. Malow, Vanderbilt  Janet Robishaw, Florida Atlantic University |
| **Sites Involved** | Geisinger and Vanderbilt University |
| **Background / Significance** | Obstructive Sleep Apnea (OSA) is a complex and heritable sleep disorder associated with a significant public health burden. Estimates suggest that 13% of men and 6% of women suffer from moderate-severe disease, with consequences that include higher risk of cardiovascular disease, cancer incidence and mortality, neurodegeneration, automobile accidents and low quality of life. As shown >20 years ago, the heritable nature of OSA accounts for a two-fold increased risk in first-degree relatives of apneics. Among the primary risk factors, genetic variants influencing soft tissue volumes, craniofacial dimensions, and obesity are implicated. Specific fat distributions, notably in the tongue, differ between obese apneics and controls, physiological mechanisms related to breathing play a role in determining risk, and craniofacial traits increase OSA risk, particularly in lean subjects. Despite this evidence, the individual genes and variants associated with OSA itself have yet to be robustly established. To discover genes and common variants associated with OSA risk, we will utilize a genome-wide (GWAS) approach. We have performed a GWAS using the MyCode Community Health Initiative data from Geisinger and case-control status for OSA. We will identify what signals are similar/different within the eMERGE data set using a similar GWAS approach. |
| **Outline of Project** | We have a validated algorithm within Geisinger for identifying OSA cases and controls based on ICD codes. We will be able to run that algorithm in the eMERGE record counter to identify OSA cases and controls for a GWAS using the eMERGE imputed data. |
| **Desired Variables**  *(essential for analysis*  *indicated by* ***\*****)* | Age  Sex  BMI  Genetically informed ancestry from principle components  OSA ICD Codes |
| **Desired Data** | Emerge I-III imputed data |
| **Planned Statistical Analyses** | Quality control for the imputed data, including imputation score cutoff and minor allele frequency (MAF) cutoff > 1%. We will drop out from the eMERGE samples any that are in the current MyCode Community Health Initiative array based data we are using at Geisinger.  Logistic regression and analyses will be adjusted for age, sex, and the number of principle components to account for ancestry.  Analyses will also be adjusted for age, sex, BMI, and principle components to identify the shift in associations when incorporating BMI as a covariate.  We may employ linear mixed models to account for relatedness between samples. We may pursue meta analysis for results we have from an OSA GWAS in Geisinger with the results of the eMERGE GWAS. |
| **Ethical Considerations** | All data will be de-identified, and only summary data will be shared in resultant manuscripts |
| **Target Journal** | PLOS Medicine, American (or European) Journal of Human Genetics, Sleep Medicine, Sleep |
| **Milestones\*\*** | Spring 2018 for completion of analyses, early Fall 2018 manuscript draft completed. Fall 2018 submission of paper. |

***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*