|  |  |
| --- | --- |
| **eMERGE Network: Proposal for Analysis**  Project/Manuscript Concept Sheet | |
| **Reference Number** | NT276 |
| **Submission Date** | March 21, 2018 |
| **Project Title** | A Phenome-Wide Association Study of Obstructive Sleep Apnea Candidate Genes |
| **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  Beth A. Malow, Vanderbilt  Janet Robishaw, Florida Atlantic University |
| **Sites Involved** | Geisinger and Vanderbilt University |
| **Background / Significance** | Obstructive sleep apnea (OSA) is a chronic condition characterized by frequent episodes of upper airway collapse during sleep. 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. Genomic variation is also implicated in some of the well-established physiological risk factors for OSA (e.g., soft tissue volumes, craniofacial dimensions, and obesity). Furthermore, there are a number of syndromes with well-defined genetic causes associated with OSA (e.g., Achondroplasia, Down syndrome, Prader-Willi syndrome, Tourette syndrome). Notably, many genes currently implicated in risk for OSA overlap with those associated with risk for co-occurring conditions in OSA. This suggests that pleiotropic genetic effects contribute to variable expression of primary symptoms and comorbidities in OSA.  Several interesting candidate variants and genes are implicated in OSA, many of which have specific hypothesized mechanisms of effect potentially useful to informing expected pleiotropic conditions. These include sleepiness-related issues for *TNFα*, craniofacial restriction for *LPAR1*, obesity mechanisms for *FTO*, and oxidative stress or cardiovascular related issues for *CYBA*. However, likely due to genetic and phenotypic heterogeneity of OSA, no genetic risk factors for OSA have been robustly established.  Given this preliminary evidence and expected pleiotropic associations, we conducted tiered analyses in the Geisinger MyCode Community Health Initiative dataset to: 1) Attempt to validate previously reported genetic associations with OSA risk by testing for associations between currently implicated variants and clinical codes for OSA (ICD9s: 327.20, 327.23, 327.29, 780.51, 780.53, 780.57 & ICD10s: G47.30, G47.33, G47.39), and 2) Conducting a Phenome-wide Association Study (PheWAS) between previously reported OSA-associated variants and 577 clinical codes as well as 143 clinical lab variables. We identified 232 significant associations, implicating 80 unique variant-phenotype pairs.  We propose to use the available sample from the eMERGE Network to conduct the same PheWAS associations of the Geisinger MyCode data to determine if signals from the Geisinger dataset generalize to the sites within the eMERGE Network. This project will represent one of the first PheWAS focused on obstructive sleep apnea-related genetic effects. The ultimate goal of this research is to identify genetic information useful to understanding the underlying etiology and heterogeneity of OSA and the common genetic pathways for influencing expression of comorbid conditions. Future endeavors may utilize this information as the basis for targeted, informed therapeutic options and a more personalized treatment approach to OSA patients. |
| **Outline of Project** | The goal of the current project is to conduct a Phenome-Wide Association Study focused on specific SNPs within candidate genes for Obstructive Sleep Apnea. Validation association studies for variants that were previously reported to be associated with OSA, and discovery PheWAS, were performed using ICD-9/ICD-10 diagnostic codes and imputed genotype information within the GHS dataset. Replication PheWAS on common variants will be conducted within independent samples from the eMERGE Network.  We expect to provide evidence that will help to decipher true from spurious genetic associations in OSA. Furthermore, we will attempt to replicate the novel genotype-phenotype associations identified via PheWAS. Results from these studies will be useful to informing both underlying genetic architecture and the causal or consequential relationships linking OSA and associated diseases. |
| **Desired Variables**  *(essential for analysis*  *indicated by* ***\*****)* | Age  Sex  BMI  Reported ancestry and genetically informed ancestry  OSA ICD Codes  Clinical lab measures matching those of our Geisinger PheWAS |
| **Desired Data** | Emerge I-III imputed data |
| **Planned Statistical Analyses** | Samples will be included if meeting the following requirements at the time of genetic data generation:  (1) 18-88 years old  (2) Available BMI  (3) Not a sample that is also within the MyCode Community Health Initiative genetic dataset  Samples will be excluded if meeting the following requirements are not met:  (1) <18 OR >88 years old  (2) Unavailable BMI  (3) Only 1 clinical code for OSA or closely-related codes (e.g., section groupings in the ICD hierarchy of ICD9: 327, ICD10: G47)  Logistic regression, linear regression, dependent on the outcome for the association  Analyses will adjusted for age, sex, and the number of principle components to account for ancestry  Analyses will also 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.*