|  |  |
| --- | --- |
| **eMERGE Network: Proposal for Analysis**  Project/Manuscript Concept Sheet | |
| **Reference Number** | NT289 |
| **Submission Date** | 5/31/2018 |
| **Project Title** | Detecting pleiotropy across neurological disorders and cardiovascular diseases via multi-trait joint association analysis |
| **Tentative Lead Investigator** *(first author)* | Xinyuan Zhang, [xinyuan.zhang@pennmedicine.upenn.edu](mailto:xinyuan.zhang@pennmedicine.upenn.edu), University of Pennsylvania |
| **Tentative Senior Author**  *(last author)* | Marylyn D. Ritchie, [marylyn@upenn.edu](mailto:marylyn@upenn.edu), University of Pennsylvania |
| **All Other Authors** | eMERGE participating sites, Yogasudha Veturi, Shefali Verma, others TBD |
| **Sites Involved** | eMERGE participating sites |
| **Background / Significance** | Neurological disorders and cardiovascular diseases are two of leading causes of death worldwide. There is increasing evidence supporting the co-morbidity between nervous and circulatory system. However, genetic contribution to this correlation is not fully understood. Part of co-morbidity can be explained by pleiotropy, since a shared pleiotropic gene/variant can potentially affect multiple phenotypes. Studies of pleiotropy could provide insights into shared genetic architecture across multiple co-morbid diseases. It could also benefit early disease intervention and drug reposition. With high-quality genotypic data and well-documented electronic health records, eMERGE network phase III can provide great perspectives in detecting pleiotropy that account for the correlation between neurological and cardiovascular diseases. |
| **Outline of Project** | 1. **Phenotype definition**   Neurological and cardiovascular phenotypes will be defined by applying “rule of three” on longitudinal ICD9 codes.   1. **Population stratification**   We plan to conduct multi-trait joint association analyses for (1) European population, (2) African American population, respectively.   1. **Genomic analyses**    1. Perform multi-trait joint association analysis on eMERGE network participating sites to detect potential pleiotropy across neurological and cardiovascular disorders   Apply functional genomic analysis on discovered pleiotropic variants to evaluate genetic architecture across neurological and cardiovascular disorders |
| **Desired Variables**  *(essential for analysis*  *indicated by* ***\*****)* | We seek the following variables for our analyses:  Primary ICD9 codes\*:   * Inflammatory diseases of the central nervous system (320-327) * Hereditary and degenerative diseases of the central nervous system (330-337) * Pain (338-338) * Headache syndromes (339-339) * Disorders of the central nervous system (340-349) * Disorders of the peripheral nervous system (350-359) * Acute Rheumatic Fever (390-392) * Chronic rheumatic heart disease (393-398) * Hypertensive disease (401-405) * Ischemic heart disease (410-414) * Diseases of pulmonary circulation (415-417) * Other forms of heart disease (420-429) * Cerebrovascular disease (430-438) * Diseases of arteries, arterioles and capillaries (440-449) * Other diseases of circulatory system (451-459)   Confounder variables\*: age, sex, and race/ethnicity  Related phenotypes\*: systolic/diastolic blood pressure, blood lipid levels, (serum cholesterol levels), serum urate levels, body-mass-index, smoking status |
| **Desired Data** | eMERGE-III HRC imputed data |
| **Planned Statistical Analyses** | 1. Perform quality control 2. Perform multi-trait joint association analysis via multi-phen software to detect potential pleiotropy 3. Evaluate the results by comparing to pleiotropic variants that identified via phenome-wide association studies 4. Apply BUHMBOX tool to filter out spurious pleiotropy 5. Perform pathway analysis on discovered pleiotropy via gene set enrichment analysis |
| **Ethical Considerations** | Genomics data and phenotypic data will be de-identified to protect confidentiality. |
| **Target Journal** | Dr. Ritchie’s UPenn start-up funds |
| **Milestones\*\*** | 1. Complete QC by early June, 2018 2. Complete analyses for identifying pleiotropic variants by June, 2018 3. Complete pathway analysis by early July, 2018 4. Write manuscript by July, 2018 |

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