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| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT416 | |
| **Submission Date** | 01/08/2021 | |
| **Project Title** | The Genetic Architecture of Diabetic Retinopathy | |
| **Tentative Lead Investigator** *(first author)* | Joseph H. Breeyear | |
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| **Tentative Senior Author**  *(last author)* | Todd L. Edwards | |
| **All Other Authors** | Ayush Giri  Dan M. Roden  Lawrence S. Phillips  Lucia Sobrin  Milam A. Brantley  Peter W. Wilson  Sabrina L. Mitchell  Yan Sun | |
| **Sites Participating** | Open to all sites  Current participants:  Vanderbilt  Million Veteran Program | |
| **Background / Significance** | Diabetic retinopathy (DR) is the leading cause of vision loss and preventable blindness in adults, afflicting an estimated 93 million individuals worldwide. As the global prevalence of diabetes mellitus (DM) rises, the global prevalence of diabetic retinopathy will also rise. Chronic disease leads to organ damage in multiple systems, such as kidney, heart, and eye. The eye is highly susceptible to damage from DM due to the delicate structures and intricate control of homeostasis in the ocular environment. DR has long been recognized as a microvascular disease, caused by the breakdown of the blood-retinal barrier, neovascularization, and increased vascular permeability in the retina. The risk factors for diabetic retinopathy include duration of diabetes, poor glycemic control, hypertension, dyslipidemia, high body mass index, and genetic risk factors. The course of diabetic disease and severity of sequelae vary substantially between cases, and the cause for this variability is not explained well by known risk factors. Several genome-wide association studies (GWAS) of DR have been completed, and while a modest number of significant loci have been reported only a single locus has been significantly associated with DR after replication. These studies were conducted in collaborative consortia of cohort studies and the largest study to date included 22,279 cases and 23,977 diabetic controls. The majority of studies focused on detecting SNP-phenotype associations and did not evaluate regulatory genetic effects or polygenic and causal effects for DR. | |
| **Outline of Project** | We will test the hypothesis that common genetic variants are associated with DR in the largest multi-ethnic GWAS to date (~74K cases, ~120K controls). We will combine evidence for association from logistic regression analysis of DR-SNP relationships across the resources described above using inverse variance-weighted fixed effects meta-analyses, both within and across racial groups.  We will use the summary statistics from the meta-analysis and the Gene-Tissue Expression Project (GTEx) in an analysis using S-PrediXcan to estimate and test effects of gene expression on DR risk. Additionally, we will test for potential causality of the significant associations discovered through the GWAS and significant associations from S-PrediXcan through the use of a colocalization analysis.  We propose to develop a DR PRS with PRSice-2 utilizing the summary statistics of the MVP GWAS and Pollock et al., followed by testing in eMERGE. PheWASs of the PRS and DR outcome can elucidate previously unknown DR risk factors. Utilizing the PRS, PheWAS results, and clinical risk factors we will develop a genome-informed predictive model that will be evaluated in the eMERGE Network. The predictive model has the potential to improve clinical management of DM and DR by identifying diabetic individuals at higher risk for developing DR. | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | Demographics  ICD9/10 codes  CPT codes  Phecodes  BMI | Common Variable Labs  Common Variable Meds  Other: Case/Control status on Phase I and Phase II phenotypes |
| **Other Desired Data *(Available from participating sites)*** |  | |
| **Desired Genetic Data** | eMERGE I-III Merged set (HRC imputed, GWAS)  eMERGE PGx/PGRNseq data set  eMERGEseq data set (Phase III)  eMERGE Whole Genome sequencing data set  eMERGE Exome chip data set  eMERGE Whole Exome sequencing data set  Other (not listed above): | |
| **Does project pertain to an existing eMERGE Phenotype?** | Yes, if so please list Diabetic Retinopathy  No | |
| **Planned Statistical Analyses** | GWAS, Meta-analysis, S-PrediXcan, S-MultiXcan, fastENLOC, PheWAS | |
| **Ethical Considerations** | None | |
| **Target Journal** | Depends on results, likely a genetics journal such as Nature Genetics or a diabetes journal | |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Gather data from all collaborators: 1-3/2021  Conduct statistical analyses: 3-12/2021  Write manuscript: 2021-2022  Circulate and submit manuscript: 2022 | |