**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Submission Date** | 7/12/2016 |
| **Project Title** | **PheWAS for functional variants in the complement system** |
| **Tentative Lead Investigator (first author)** | Krzysztof Kiryluk |
| **Tentative Senior Author (last author)** | Ali Gharavi |
| **All other authors** | Joshua Denny, George Hripcsak, Chunhua Weng, Ning Shang, Scott Hebbring, *any additional eMERGE members interested in participating* |
| **Sites Involved** | We propose a network-wide study (all sites invited to participate). |
| **Background / Significance** | Our group has been interested in the genetic regulation of the complement system and this study will test the known GWAS variants in the complement genes for pleiotropic effects phenome-wide.  Complement system provides a primary defense mechanism against encapsulated organisms including *Neisseria* species. However, uncontrolled activation of the complement system may lead to increased inflammation and tissue injury with serious multi-organ manifestations. For example, complement activation plays a critical role in the pathogenesis of septic shock and vascular thrombosis; activation of the complement system in the kidney leads to vascular injury and various forms of glomerulonephritis, including lupus nephritis (LN), mesangioproliferative glomerulonephritis (MPGN), post-streptococcal glomerulonephritis (PSGN), and IgA nephropathy (IgAN); activation of complement in the retina is involved in the pathogenesis of age-related macular degeneration (AMD). There are also rare genetic disorders due to mutations in specific complement regulatory genes. For example, mutations in CFH cause C3 glomerulonephritis (C3GN), dense deposit disease (DDD), and atypical hemolytic uremic syndrome (aHUS).  Recent GWAS and sequencing studies have identified a number of functional variants in the complement genes that have specific disease associations, including for AMD, SLE, IgAN, and Neisseria infections. Quantitative GWAS of circulating complement components (e.g. plasma C3, C4, or C5 levels) identified a number of additional regulatory loci, but their disease associations are not yet known. The goal of this study is to systematically characterize pleiotropic effects of these variants using EHR-based PheWAS approach. |
| **Outline of Project** | The project will involve the following steps:   1. Manual curation of common variants in the complement pathway genes with established GWAS disease associations (done by Columbia site, with input from other sites) 2. EMERGE Network-wide PheWAS for these variants (Columbia site with input from the DCC and other EMERGE sites) 3. Manuscript preparation and submission |
| **Desired**  **Variables**  **(essential for analysis**  **indicated by \*)** | This study involves PheWAS analysis of ICD and procedure codes for all EMERGE participants. The required variables include:   * ICD9/10 codes for PheWAS network-wide\* * Age, sex, race/ethnicity, cohort/site\* |
| **Desired Data** | * Genotypes for selected variants (genotyped or imputed)\* * Genetic ancestry information (for ancestry adjustment in PheWAS). |
| **Planned Statistical Analyses** | We will perform PheWAS analysis for ~20 variants in 10 complement genes, including all previously described disease-associated variants in *CFH, CFHR1/3, CFB, C2, C3, C4, C5, C9, ITGAM, ITGAX.* We will (1) replicate known associations for these genes, (2) discover their new pleiotropic effects, and (3) examine shared phenotypic associations between these loci. |
| **Ethical considerations** | There are no additional risks involved. The EMR and genomic data will be stored at a secured location in the data storage system at Columbia University. No data will be shared with unauthorized third parties. Patient identity will not be compromised by the proposed analysis. We will also abide by the EMERGE guidelines in this regard. |
| **Target Journal** | TBD, depending on the findings |
| **Milestones\*\*** | Total Duration of the study: 6 months  Implementation of PheWAS: 3 months  Draft of manuscript to authors: November 2016  First submission: December 2016 |

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