**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Submission Date** | January, 31 2017 |
| **Reference Number** | NT211 |
| **Project Title** | The Genetic Architecture of Auto-Inflammatory and Auto-Immune Diseases |
| **Tentative Lead Investigator (first author)** | Patrick Sleiman |
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| **Sites Involved** | All |
| **Background / Significance** | Autoinflammatory diseases (AIDs) refers to a group of hereditary inflammatory and autoimmune conditions affecting multiple organ systems, usually recurrent and without evidence of infection. Awide range of diseases meets this definition asz listed below. Studies have identified candidate genes that are associated with several AIDs, some of which are shared across clinically-distinct disease groups. To investigate the genetic architecture across common AIDs, we propose a heterogeneity sensitive GWAS (hsGWAS) across numerous diseases in a nested case-control study. The methodology will replicate and extend a similar study by our group on auto-immune diseases (PMCID: PMC4863040). |
| **Outline of Project** | To identify shared AID associations, we will first perform a “classic” GWAS by merging all disease cases in a single case-control association study design. Next, we will use a heterogeneity-sensitive GWAS “hsGWAS” approach, where for each SNP commonly genotyped or imputed and passing QC across all disease cohorts, we search for the best disease model among all AID combinations. For each model, cases included are assigned as the overall model cases, and cases belonging to other AIDs, either relabeled as controls or excluded during association testing. We then test each SNP for association with case-control status enumerative across the modeled disease combinations, using a discrete local maximum method (DLM) to control for Type-I error introduced by multiple testing as previously described. |
| **Desired**  **Variables (essential for analysis**  **indicated by \*)** | Autoimmune Thyroiditis (including Graves and Hashimoto)  Behcets Disease  Celiac Disease  Type-1 Diabetes  SLE  Ankylosing Spondylitis  Psoriasis  Rheumatoid Arthritis  Multiple Sclerosis  Atopic Dermatitis  Vitiligo  Alopecia  Asthma  Crohn’s Disease  Ulcerative Cholitis  Sarcoidosis  CVID  **Chronic Rhinosinusitis**  **Chronic Dermatomyocitis**  Juvenile Systemic Granulomatosis (aka Blau syndrome, Pediatric Granulomatous Arthritis (PGA)  Chronic Serous Otitis Media  **Chronic Rhinitis and Rhinoconjunctivitis**  Systemic-Onset Juvenile Idiopathic Arthritis (SoJIA) (aka Still’s, Systemic  Juvenile Idiopathic Arthritis) |
| **Desired data** | eMERGE 1,2,3 phenotype data on the above phenotypes  dbGaP dataset |
| **Planned Statistical Analyses** | Meta-analysis of hsGWAS for the respective studies; analyses of genetic sharing and heritability across these diseases |
| **Ethical considerations** | None |
| **Target Journal** | Nature Genetics/Nature Medicine |
| **Milestones\*\*** | Development of (basic) phenotype algorithm: 3/31/17  Validation of phenotype algorithm: 4/28/17  Implementation of (basic) phenotype algorithm: 6/30/17  Analyses of array data: 9/30/17  Draft 1 of manuscript: 11/31/17  Submission of manuscript: 12/31/17 |