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| **External Collaborator Proposal** *for* **eMERGE Network Analysis**Project/Manuscript Concept Sheet |
| **Reference Number** | NT229 |
| **Submission Date** | 4/26/2017 |
| **Tentative Lead Investigator** *(first author with contact information and affiliation)* | Xinyuan Zhang, xzhang2@geisinger.eduYuki Bradford, ybradford@geisinger.edu |
| **Tentative Senior Author** *(last author)* | Marylyn D. Ritchie, mdritchie@geisinger.edu |
| **eMERGE Site Sponsor & Contact** | Geisinger Health System, Marylyn Ritchie |
| **Project Title** | eMERGE GWAS for GIANT meta-analysis |
| **All Other Authors**  | TBD |
| **Other eMERGE Sites Involved** | All eMERGE network |
| **Background / Significance** | Obesity is globally prevalent and has an increasing risk for multiple disorders, including cardiovascular diseaseand Type II diabetes1,2. Nearly 40-70% of variability in body mass index (BMI), a measure which used to assess obesity, has been attributed to genetic component3. Genome-wide estimates imply that common variant explains for >20% of BMI variation4. Previously identified loci only account for a limited fraction of variation in BMI4 and sample size is a key factor to increase power to discover associated variants5. Genetic Investigation of Anthropometric Traits (GIANT) consortium is establishing large-scale meta-analysis resources for BMI GWAS. With well-documented EHR and genotyped genomics data, eMERGE network phase III provides great perspectives addressing the challenge and assists to explain heritability in obesity. |
| **Outline of Project** | 1. **Phenotypic modeling**

Genotyped participants of all eMERGE sites (except for the ones who is younger than 18 years old, pregnant women and carry Mendelian disease) will be used in our study. BMI will be adjusted for ethnicity, sex and disease status in a linear regression model. All phenotypic traits will be inverse normal transformed after creation of residuals to facilitate proper analysis of low frequency variants. 1. **Population stratified grouping**

We plan to conduct a series of genome-wide association studies for (1) all ancestries, (2) European men, (3) European women, (4) European population, respectively.1. **Genomic analyses**
2. Use eMERGE network GWAS results to calculate the common variant heritability for BMI
3. Perform meta-analysis using our GWAS results and GIANT studies together to re-validate and define novel associated variants.
4. Apply functional genomic analysis on discovered variants to evaluate potential biological link to obesity -susceptibility.
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| **Desired Variables** *(essential for analysis**indicated by* ***\*****)* | We seek the following variables for our analyses:* Primary phenotypes\*: Computed anthropometric traits (Height (cm), Body Mass Index: mass(kg)/height2(m2), Waist-to-Hip (waist/hip circumference(cm)) Ratio adjusted for BMI, Waist-to-Hip Ratio unadjusted for BMI)
* Confounder variables\*: age at measurement, year of birth, sex, and race/ethnicity
* Related disease status\*: coronary artery disease, type II diabetes
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| **Desired Data** | eMERGE-III HRC imputed data |
| **Planned Statistical Analyses** | 1. Imputation and quality control separately for different genotyping array.
2. eMERGE genome-wide association analysis using linear regression.
3. Meta-analysis using METAL.

Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA) and DEPICT to identify overrepresented gene sets. |
| **Ethical Considerations** | Genomics data and phenotypic data will be de-identified to protect confidentiality.  |
| **Available Funding or Resources** | eMERGE |
| **Milestones\*\*** | 1. Complete QC by mid-April
2. Complete association analyses by April 30 (pending receipt of phenotype data and genotype imputation on HRC by David Crosslin)
3. Write relevant portions of the manuscript by end of Spring 2017.
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***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*

1. Lewis, Cora E., et al. "Mortality, health outcomes, and body mass index in the overweight range." *Circulation* 119.25 (2009): 3263-3271.
2. Pi-Sunyer, F. Xavier, et al. "Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults." *American Journal of Clinical Nutrition*68.4 (1998): 899-917.
3. Maes, Hermine HM, Michael C. Neale, and Lindon J. Eaves. "Genetic and environmental factors in relative body weight and human adiposity." *Behavior genetics*27.4 (1997): 325-351.
4. Locke, Adam E., et al. "Genetic studies of body mass index yield new insights for obesity biology." *Nature* 518.7538 (2015): 197-206.

Speliotes, Elizabeth K., et al. "Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index." *Nature genetics*42.11 (2010): 937-948.