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| **Reference Number** | NT359 |
| **Submission Date** | September 12, 2019 |
| **Project Title** | Identify pleiotropy between anthropometric traits and a wide range of traits and diseases from EHR |
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| **Tentative Senior Authors** *(last author)* | Eirini Marouli, Sonja Brendt, Ruth Loos, Kari North, Joel Hirschhorn  |
| **All Other Authors**  | TBD |
| **Sites Involved** | Geisinger, all welcome |
| **Background / Significance** | * To date, researchers have had great success using genome-wide association studies (GWAS) of obesity-related anthropometric traits.1-5 Despite the growing body of literature on the genetic architecture of obesity-related traits,3,5-17 several questions remain that result in a poor understanding of the mechanisms by which obesity leads to the cascade of negative health outcomes. The elevated burden of disease imposed by obesity is of great concern as rates of obesity have more than doubled across the globe over the past three decades.18-20 Thus, we propose to leverage existing phenomic and genomic resources in eMERGE, to explore the causal relationships between susceptibility variants for height, BMI, waist-to-hip ratio identified in the current GIANT consortium efforts with related disease outcomes and risk factors. Through combining the high-throughput hypothesis generating method of phenome-wide association study (PheWAS) and Mendelian Randomization (MR), there is an opportunity for new discoveries of the impact of obesity on health outcomes.
* Analyses will include PheWAS/MR results on significant variants identified by GIANT meta-analysis and perform associations with several traits including diagnosis codes and clinical lab measures. Especially, EHR further aids in exploration and discovery of novel genotype-phenotype relationships and potential pleiotropy i.e., finding of multiple independent phenotypes associated with anthropometric trait susceptible variants.
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| **Outline of Project** | * This request is part of a multi-consortium collaboration between GIANT, Geisinger, and eMERGE to 1) investigate potential pleiotropy of significant risk variants, pertaining to height/BMI/waist-to-hip ratio identified from GIANT 1KG-HRC meta-analysis of greater than 1 million individuals; 2) conduct bi-directional MR to assess the causal direction of any identified cross-trait associations and compare results across other datasets contributing to GIANT for validation.
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| **Desired Variables** *(essential for analysis**indicated by* ***\*****)* | * Based on the availability of height/BMI/waist-to-hip ratio measures, consented participants will potentially contribute to these analyses.
* Age at first measure/diagnosis
* Sex
* All phenotype-relevant covariates will be considered such as requiring procedures, clinical labs, physical measures, and all ICD-9/10 codes and vitals from eMERGE.
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| **Desired Data** | Emerge I-III imputed dataTargeted exome sequencingCNV calls All ICD/CPT codes, demographics, lab values, Principal Components. |
| **Planned Statistical Analyses** | Quality control for the imputed data, including imputation score cutoff. We will drop out any eMERGE samples that are in the current DiscovEHR data we are using at Geisinger.* All PheWAS analyses, assuming an additive genetic model, are standard logistic (categorical, e.g. ICD-9/10 codes, CPT codes) or linear (continuous traits, e.g. lab values, physical measures) regression methods.
* Analyses may be performed stratified by sex, and ancestry, and adjusted for center (where appropriate), age at first measure/diagnosis, and principal components to control for ancestry.
* We will use a MR statistical approach to then infer causal relationships between anthropometric traits (i.e. height and BMI) and their most statistically associated cross-traits and -conditions. This statistical approach provides information on the shared co-occurrence of traits based on shared genetics, clarifying the direct relationship between two co-occurring traits.
* Secondary analyses and fine-mapping attempts may include sequencing resources.
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| **Ethical Considerations** | All data will be de-identified, and only summary data will be shared in resultant manuscripts |
| **Target Journal** | TBD (e.g. Nature, Nature Genetics PLOS Genetics, American (or European) Journal of Human Genetics) |
| **Milestones\*\*** | October 2019 for concept sheet approval; March 2020 for completion of PheWAS/MR analyses, July 2020 manuscript draft. September 2021 for second draft of paper, October 2021 for submission of paper.  |

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

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