Application number/Title: 11898 - Genetic studies of anthropometric traits and methods for analysis of multiple phenotypes

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Keywords provided by the Applicant PI to describe the research project:

Obesity, Growth, Genetics, Methodology, Pathways

Application Lay Summary:

1a: Our major ongoing research aim is to understand the genetic basis of anthropometric traits, including anthropometric measures of obesity and of skeletal growth. The health conditions relevant to these traits are obesity and its metabolic complications, such as diabetes, and also abnormalities of skeletal growth such as short stature. We have previously identified hundreds of loci associated with these traits, providing insights into genetic architecture and novel biology. We aim to extend these studies using data from the UK Biobank. We also plan to use these data to extend ongoing efforts to develop methodologic approaches to analyzing multiple phenotypes simultaneously.

1b: Our work would combine the UK biobank data with large ongoing efforts in the GIANT consortium to greatly advance our understanding of the genetic basis and biology of obesity, a major risk factor for common illnesses in society, and of the genetic basis and biology of normal skeletal growth. Improved understanding could yield better predictive biomarkers or guide future therapeutic development for obesity, and also potentially diseases of abnormal skeletal growth. Our methodological work and our work on height, a model polygenic trait, would inform genetic studies of many important polygenic diseases.

1c: We will perform genetic association analysis (similar to prior work we have helped lead for anthropometric traits). In this approach, we use well-established statistical methods to systematically search for genetic variants that affect measures of obesity (such as body mass index) or of anthropometric traits skeletal growth (such as adult height). We will also use more complex statistical methods designed for analysis of multiple traits simultaneously, and test whether

these new methods improve our power to discover these genetic variants, and also whether they can better classify variants and biological pathways by their effect on human traits.

1d: We would analyze the full cohort.

PROJECT EXTENSION APPROVED 07/09/2017:

"Blood cell traits were already added in a previous amendment for replication of results so is a logical extension. We plan to perform a complete genome-wide association study for all static blood cell traits available in the UK Biobank population to gain further insight into human hematopoiesis. This includes analysis of 16 blood cell traits, including red blood cell counts, platelet counts, and white blood subtype cell counts. We will examine genetic correlations among traits, perform genetic fine mapping, and perform overlap with functional genomic data we have produced, such as through the use of open chromatin analyses across the human hematopoietic hierarchy with ATAC-sequencing. We are performing this analysis in collaboration with and in a coordinated manner with other groups doing similar analyses, including the groups of Nicole Soranzo, Guillaume Lettre, and Alex Reiner."