Title: **Genetics of Metabolically Healthy Obesity**

Lead: Shengxu Li (PI)

Mechanism: NIH RO3

Budget: $100,000 (direct cost)

Deadline: February 5, 2015

Proposed specific aims

Obesity is a major public health challenge due to its high prevalence and associated morbidity and mortality. An increasing body of evidence has shown that the health consequences of obesity are heterogeneous, such that not all obesity individuals display cardiometabolic abnormalities. Obesity without accompanying cardiometabolic abnormalities has been called “metabolically healthy obesity (MHO)”. The underlying mechanisms for such heterogeneity is not well understood. It is hypothesized that genetic factors may contribute to MHO. As an example, variants near insulin receptor substrate 1 (IRS-1) gene are associated with increased adiposity but decreased risk of cardiometabolic abnormalities. However, our understanding of MHO etiology is still very limited. Taking advantage of available GWAS data to explore genetic basis of MHO is a powerful, yet very cost-efficient approach.

The main objective of this project is to examine the associations of common genetic variants and MHO phenotype. To accomplish this goal, we will take advantage of publically available database dbGAP hosted by National Institutes of Health. We will examine the associations of common variants and MHO phenotype in >50,000 individuals available in the dbGAP database. Identified promising variants will be taken forward for replication in studies participating in the GIANT Consortium with relevant data available. GIANT consortium is a large-scale international effort to examine genetic bases of anthropometric traits with more than 500,000 participants. Replicated variants will be further validated in the well-characterized cohort – the Bogalusa Heart Study, which has detailed cardiometabolic phenotypes from childhood to adulthood.

1. **Specific Aim 1:** Examine the associations of common genetic variants (minor allele frequency > 1%) and MHO phenotype in dbGAP participants. We will use logistic regression model to examine such associations. MHO will be defined as BMI > 30kg/m2 without cardiometabolic abnormalities (dyslipidemia, hypertension, and insulin resistance). We will focus on additive genetic models. We will take forward promising variants for replication in **Specific Aim 2**
2. **Specific Aim 2:** Replicate promising variants identified in **Specific Aim 1** in >300,000 participants from studies of the GIANT consortium. We will validate replicated variants in studies of the GIANT consortium with relevant data. Replicated variants will be further validated in the Bogalusa Heart Study in **Specific Aim 3**.
3. **Specific Aim 3:** Validate replicated variants in **Specific Aim 2** in the Bogalusa Heart Study. We will examine the associations of replicated variants with MHO phenotype development from childhood to adulthood in 1200 Bogalusa Heart Study participants who have been examined for more than four decades beginning in childhood.

**Public health relevance:** Exploring genetic basis of MHO will help elucidate the underlying mechanisms for the adverse effects of obesity and help translate these findings into biological insights, clinical and public health practice.