Title: **Integration of Genetics and Epigenetics in Obesity and Related Metabolic Traits**

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Mechanism: NIH RO1

Budget: ~$900k for five years

Deadline: Oct 5, 2014

Proposed specific aims (see next page)

**Integration of Genetics and Epigenetics in Obesity and Related Metabolic Traits**

Cardiometabolic abnormalities, including obesity, insulin resistance, dyslipidemia and hypertension, have been widely recognized as risk factors for cardiovascular disease and type 2 diabetes. Recent genome-wide association studies (GWAS) have identified a large number of genetic loci related to these traits. However, the majority of these loci only explain a small fraction of phenotype heritability and do not have known functions, rendering them of limited use in the clinic. Most recently, emerging evidence suggests that epigenetics may play an important role in the cardiometabolic complications and related cardiovascular disease. Moreover, recent epigenome-wide association studies (EWAS) in type 2 diabetes, as well as ours in obesity, revealed that genes harboring differentially methylated CpG sites displayed significant enrichment of GWAS loci previously identified for these two disorders. Therefore, we hypothesize that the cardiometabolic GWAS loci represent a group of key genes in the cardiometabolic regulation pathways, in which either genetic or epigenetic (e.g. DNA methylation) variations, or their composition, contribute to the cardiometabolic abnormalities.

The main objective of this project is to demonstrate the effects of DNA methylation variations and sequence variants in the cardiometabolic GWAS genes on the development of cardiometabolic abnormalities, dependently or independently. To accomplish this goal, we will take advantage of two existing cohorts, the Georgia Prevention Cohort (GPC) and the Bogalusa Heart Study (BHS), both with detailed cardiometabolic phenotypes and peripheral blood leukocyte DNA samples stored. We will examine 1,064 Caucasian-American youth and young adults (aged 13-27) from the GPC, in which 450 subjects were assessed in multiple visits during an 11-year period. We will also examine 800 Caucasian-American young adults (aged 22-45) from the BHS; all of them will have a second visit an average of 8 years apart and the DNA samples will be collected. In total, we will examine the methylation variations and sequence variants in the cardiometabolic GWAS genes in 1864 Caucasian-American subjects at baseline and re-examine the methylation variations in 2/3 of them (N=1250) after an 8- or 10-year period.

The target enrichment sequencing technology will be applied in DNA samples of 1864 Caucasian-American youth and young adults from the GPC and the BHS. With these data, our **Specific Aims** are:

1. Examine the associations of methylation variations and sequence variants with cardiometabolic traits and disentangle their interplay. A series of linear regression models will be performed to test the associations between methylation variations and cardiometabolic traits, between sequence variants and cardiometabolic traits, as well as between sequence variants and methylation variations. We will adopt a multistep procedure recently developed to elucidate the relationships among sequence variants, methylation variations and cardiometabolic abnormalities.
2. Examine the potential causal effect of methylation variations on the development of cardiometabolic abnormalities. The top signals of cardiometabolic methylation variations identified in aim 1 will be re-examined in 1250 subjects at both baseline and last visit using a custom chip. A cross-lagged path model will be performed to dissect the complex relationship between change patters of methylation variations and cardiometabolic traits over time.

In the **secondary aim**, we will examine whether our findings are gender-dependent. In addition, since GWAS loci were discovered mainly based on Caucasian-American population, this project will use Caucasian-American subjects only. However, the GPC included 1243 African-Americans (AA) and the BHS included 420 AAs. As another secondary aim, we will validate our findings in AA population using the custom chip.

**Public health relevance:** Integration of epigenetic and genetic variations in specific cardiometabolic GWAS genes and use of a longitudinal study design will provide potential causality mechanisms underlying these genes contributing to cardiometabolic abnormalities, and help to translate promising genomic discovery into biological insights, clinical and public health practice.