CPT1A Methylation is a Novel Epigenetic Marker of Cardiovascular Risk


Introduction: Inter-individual variability in plasma lipid levels and other cardiovascular risk phenotypes is influenced by both genetic and environmental factors. However, known predictors explain only a limited portion of the observed variability. We hypothesized that epigenetic changes such as DNA methylation contribute to the architecture of complex metabolic traits such as plasma lipids and thus affect cardiovascular risk.

Methods: We isolated DNA from CD4+ T-cells and quantified methylation at 461,281 CpG sites using the Infinium HumanMethylation450 BeadChip Kit in 888 participants of the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study. Participants were randomly allocated to either discovery (n=593) or replication (n=295) data subsets. In the discovery stage, we modeled percent methylation at each CpG site as a function of fasting plasma lipids and adiponectin using mixed linear regression models adjusted for age, gender, study site, cell purity, and family structure. After applying a Bonferroni correction for multiple testing, we evaluated all markers that reached statistical significance for association with the trait of interest in the replication data set.

Results: In the discovery stage, methylation at two intronic CpG sites (cg00574958 and cg17058475) of the gene encoding carnitine palmitoyltransferase 1A (CPT1A), a key enzyme in lipid metabolism, was strongly associated with triglyceride levels (P= 5.3x10-14 and 1.2x10-9 respectively) and very low-density lipoprotein (VLDL) cholesterol levels (P<1.0x10-8). Additionally, we found robust associations between methylation in cg00574958 in CPT1A and plasma adiponectin (P<1.0x10-9). We successfully replicated the associations with triglycerides and adiponectin (P<1.0x10-6).

Conclusions: We have identified differential DNA methylation in CPT1A as a novel contributor to inter-individual variability in plasma triglycerides, VLDL cholesterol, and adiponectin. Our findings lay the groundwork for incorporating epigenetic data in cardiovascular risk stratification, disease prevention, and treatment strategies.