

# Dnmt3l: A New Genetic Factor in Obesity

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Acetylation and methylation are garnering increasing attention for their respective roles in metabolic regulation through altering both gene expression and cytoplasmic enzyme activity. However, despite the metabolic underpinnings of obesity, little work has been done to elucidate the impacts of these processes on adiposity and the genetic networks through which they act. We utilize clinical phenotype and mRNA expression data in F2 hybrid BTBRxC57BL/6J mice to determine the most active genes in this network, and propose a chromosomal locus on which they are regulated. Expression of the DNA methyltransferase homolog Dnmt3l, known to regulate de novo methylation, is revealed to be highly correlated with obesity-related phenotypes, suggesting a regulatory role in adipocyte proliferation. We likewise study several other genes which show significant effects on adiposity in the dataset--some with known roles regulating such phenotypes, others not previously implicated--including Acl, Otop1, Pla2g2e, and Gm6484. Quantitative trait locus (QTL) analysis reveals that the region on mouse chromosome 5 in the neighborhood of 54.74 cM strongly regulates both adiposity phenotypes and the expression of most genes under consideration, notably Dnmt3l. Bayesian analysis on gene expression and phenotype data with R/qtlnet suggests that the genes Parm1 and Epgn have a major regulatory role in adiposity, mediated largely by Dnmt3l and its associated genes. These links emphasize the need for greater understanding of Dnmt3l and the role of ongoing histone methylation and acetylation (both of histones and enzymes within the cytoplasm) in the metabolic patterns leading to increased lipid deposition, and offer hope for predictive genetic testing of obesity.

## Awards Won:

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