Mouse-Human Experimental Epigenetic Analysis Unmasks Dietary Targets and Genetic Liability for Diabetic Phenotypes

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Technology description

Using a functional approach to investigate the epigenetics of type 2 diabetes (T2D), we combine three lines of evidence—diet-induced epigenetic dysregulation in mouse, epigenetic conservation in humans, and T2D clinical risk evidence—to identify genes implicated in T2D pathogenesis through epigenetic mechanisms related to obesity. Beginning with dietary manipulation of genetically homogeneous mice, we identify differentially DNA-methylated genomic regions. We then replicate these results in adipose samples from lean and obese patients pre and post-Roux-en-Y gastric bypass, identifying regions where both the location and direction of methylation change are conserved. These regions overlap with 27 genetic T2D risk loci, only one of which was deemed significant by GWAS alone. Functional analysis of genes associated with these regions revealed four genes with roles in insulin resistance, demonstrating the potential general utility of this approach for complementing conventional human genetic studies by integrating cross-species epigenomics and clinical genetic risk.

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