**Adipose ADH1B as a global modulator of "obeso-insulin resistance" in multiethnic populations.**

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**Introduction.**

Type 2 diabetes (T2D) is a complex metabolic disease that is more prevalent in ethnic groups such as Mexican Americans, and is strongly associated with the risk factors obesity and insulin resistance. The goal of this study was to detect complex disease predisposing genes using the technique of whole genome gene expression analysis, also known as transcriptomics. We performed transcriptomic analysis of gene expression in adipose tissue biopsies from a Mexican American population cohort from San Antonio, Texas, to detect common patterns of gene regulation associated with obesity and insulin resistance. We detected a novel gene, alcohol dehydrogenase 1B (ADH1B) which has not previously been recognized as a candidate gene for obesity, insulin resistance, or T2D.

**Methods.**

Basal fasting RNA was extracted from adipose tissue biopsies from 75 unrelated individuals, and gene expression data generated on the Illumina BeadArray platform. The number of gene probes with significant expression above baseline was approximately 31,000. We performed multiple regression analysis of all probes with 15 key metabolic traits. We investigated the causal functional relationship between ADH1B expression and intracellular correlates of obesity and insulin resistance using ADH1B gene knockdown in human adipocyte primary culture. We performed a meta-analysis of ADH1B gene expression correlation with obesity and insulin resistance in 3 additional human population cohorts: Pima Indians from Arizona, African Americans from Wake Forest University and Europeans from the TwinsUK study.

**Results.**

ADH1B mRNA expression was highly correlated with insulin resistance traits in multiple human populations. Its expression was reduced in obesity, an insulin resistant state. It was causally related to insulin signaling and its expression (reduced by obesity or ADH1B knockdown) was stimulated by insulin. Knockdown of ADH1B was associated with decreased insulin-mediated glucose uptake. Inhibition of AKT, a component of the insulin signaling pathway, was associated with decreased expression of ADH1B.

**Conclusions:**

ADH1B represents a global modulator of obese insulin resistance in multiple human populations.

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