TRANSCRIPTIONAL REGULATION OF THE HUMAN ALCOHOL DEHYDROGENASES AND ALCOHOLISM

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Abstract:

Alcohol dehydrogenase (ADH) genes encode proteins that metabolize ethanol to acetaldehyde. Humans have seven ADH genes in a cluster. The hypothesis of this study was that by controlling the levels of ADH enzymes, cis-regulatory regions could affect the risk for alcoholism. The goal was thus to identify distal regulatory regions of ADHs. To achieve this, sequence conservation across 220 kb of the ADH cluster was examined. An enhancer (4E) was identified upstream of ADH4. In HepG2 human hepatoma cells, 4E increased the activity of an ADH4 basal promoter by 50-fold. 4E was cell specific, as no enhancer activity was detected in a human lung cell line, H1299. The enhancer activity was located in a 565 bp region (4E3). Four FOXA and one HNF-1A protein binding sites were shown to be functional in the 4E3 region. To test if this region could affect the risk for alcoholism, the effect of variations in 4E3 on enhancer activity was tested. Two variations

had a significant effect on enhancer activity, decreasing the activity to 0.6-fold. A third variation had a small but significant effect. The effect of variations in the ADH1B proximal promoter was also tested. At SNP rs1229982, the C allele had 30% lower activity than the A allele. In addition to studying the regulatory regions of ADH genes, the effects of alcohol on liver-derived cells (HepG2) were also explored. Liver is the primary site of alcohol metabolism, and is highly vulnerable to injuries due to chronic alcohol abuse. To identify the effects of long term ethanol exposure on global gene expression and alternative splicing, HepG2 cells were cultured in 75 mM ethanol for nine days. Global gene expression changes and alternative splicing were measured using Affymetrix GeneChip® Human Exon 1.0 ST Arrays. At the level of gene expression, genes involved in stress response pathways, metabolic pathways (including carbohydrate and lipid metabolism) and chromatin regulation were affected. Alcohol effects were also observed on alternative transcript isoforms of some genes.

Description:

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