Title

USE OF DNA PROBES TO INVESTIGATE MOLECULAR GENETIC CHANGES IN ALCOHOL-DEHYDROGENASE (ADH) AND LINKED GENES IN HUMAN HEPATOMAS

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MOLECULAR GENETICS OF ALCOHOL-METABOLIZING ENZYMES: Akira Yoshida, Department of Biochemical Genetics, Beckman Research Institute of the City of Hope, Duarte, California 91010, USA

Three genes for ADH (Class I) are on chromosome-4. These genes have a similar organization and a high degree of resemblance (about 95%) in their coding sequences, suggesting the recent divergence of these loci. However, each of the three subunits and the Oriental-type subunit has unique structures in the vicinity of the active kinetic properties. The size heterogeneity and developmental changes of expression were observed in their mRNA.

The gene for the cytosolic $ALDH_1$ is on chromosome-9, and that for the mitochrondrial $ALDH_2$ is on chromosome-12. The degree of resemblance between the two is 66% at the cDNA level and 69% at the protein level. The $\underline{ALDH_2}$ gene is about 45 kbp long and contains 13 exons which encode 517 amino acid residues. The Oriental atypical $ALDH_2^2$, associated with diminished catalytic activity, has a base transition in the 12th exon, resulting in a Glu→Lys substitution at the 14th position of the COOH-terminal. Using specific synthetic oligonucleotide probes, genotypes of the ADH and ALDH loci of Japanese with alcoholic liver diseases were determined. Strong association of the diseases with $\underline{ALDH_2^1}$ was found. Genetic background of other alcohol-related problems can be explored by this approach.

Inducible, NADP-specific Rat Aldehyde Dehydrogenases: A Novel Structural Type. John Hempel, Kim Harper and Ronald Lindahl. Univ. of Pittsburgh and Univ. of Alabama

NADP-specific rat AlDHs induced in hepatocellular carcinoma and by TCDD treatment are identical, 452 amino acid chains. Relative to 500-residue NAD•AlDHs of human/equine/bovine liver cytosol/mitochondria (with minimum ~70% positional identity) the N-terminus is at position 57 and the C-terminus extends 16 residues beyond that of NAD•AlDH. Vs. human E_1 identities at 127/437 positions (29%) are achieved after placement of 9 gaps (totalling 15 positions) in NADP•AlDH and 2 gaps (7 positions) in E_1. Identites are well spread across the alignment, with some degree of clustering in positions 186–245 of E_1. This segment encompasses presently identified active site residues of NAD•AlDH, Cys-302 and Glu-268, and the putative coenzyme-binding fold identified by Gly distributions. Only one other cysteine residue is conserved vs. E_1 or E_2: Cys-275. Many predicted reverse turns occur in comparable segments, some not conserved in sequence. Conservation of tertiary structure is also implicated by the high conservation of glycine residues (20/48 in E_1), often required sterically for chain bending. These characteristics indicate a clear but distant relationship between NADP•AlDHs and NAD•AlDH and reveal a new class of this enzyme. Supported by AA06985

USE OF DNA PROBES TO INVESTIGATE MOLECULAR GENETIC CHANGES IN ALCOHOL DEHYDROGENASE (ADH) AND LINKED GENES IN HUMAN HEPATOMAS.
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Availability of DNA probes has allowed us to define the chromosomal assignment, genetic variation and genetic linkage relationships of human ADH. Gene probes have also been used to examine the molecular genetic basis of altered expression of ADH in different tissues at different stages of fetal development and in human hepatomas. We mapped ADH genes to the region 4q21-4q25. ADH genes are genetically closely linked to the epidermal growth factor (EGF) gene. ADH genes are also linked at a greater distance to the genes for albumin and alpha fetoprotein. These linkage relationships are of particular interest in light of the altered expression of albumin, alpha fetoprotein and ADH in hepatomas and the important role of epidermal growth factor and its receptor (EGFR) in the growth and regeneration of liver cells. Our studies demonstrated that deletions occur on one member of the chromosome 4 pair in a significant proportion of hepatomas leading to allele loss of ADH and/or EGF and certain other 4Q markers. We are examining other regions of the genome of hepatomas for allele loss. At this time, the only other chromosome region in which we have demonstrated allele loss is in the EGFR region, chromosome 7p1.

BIOCHEMICAL AND MOLECULAR GENETIC STUDIES RELATED TO CHANGES IN ALDEHYDE DEHYDROGENASE ISOZYMES IN ALCOHOLISM
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A comparative biochemical and molecular genetic study of human liver and erythrocyte ALDH was undertaken to elucidate the cause and mechanism underlying the loss in ALDH enzyme activity in alcoholism. We have previously reported that there is a considerable similarity in biochemical and molecular properties of human liver cytosolic aldehyde dehydrogenase and erythrocyte aldehyde dehydrogenase (ALDH). According to our earlier studies a significant depletion in liver and erythrocyte ALDH activity takes place in chronic alcohol abuse. A lack of correlation between reduced erythrocyte ALDH activity and the degree of alcohol-related liver damage was observed.

The results to be presented indicate that altered catalytic, molecular and immunological properties of red cell ALDH in acute and chronic alcohol abuse represent an inactivation of the enzyme molecules and not a suppressed synthesis of the enzyme. An involvement of a disturbed glutathione metabolism in the loss of ALDH activity in alcohol abuse is currently being investigated since our preliminary results indicate a significantly lower red cell glutathione concentration in alcoholics.