ANNALS of Hepatology

HEPATOLOGY HIGHLIGHTS

November-December, Vol. 12 No.6, 2013: 860

Alcohol, liver and genes: an intricate puzzle

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Genetic factors affecting susceptibility to alcoholic liver disease in an Indian population

Kumar DA. Alcoholic liver disease (ALD) results from a complex interaction between behavioral, environmental, and genetic factors. Although several studies have defined a close relationship between cumulative alcohol intake and risk of developing liver damage, extensive individual variability exists in disease susceptibility. Even among heavy drinkers (more that 100 g alcohol per day), only some individuals develop clinical, biochemical, and histological signs of ALD, ranging from 5-40% in the different series. The importance of genetic factors in the predisposition to ALD has long been recognized. Genes encoding for enzymes with alcohol dehydrogenase (ADH2, ADH3) and aldehyde dehydrogenase (ALDH2) activities, for components of the microsomal ethanol oxidation system (cytochrome P4502E1), or for proteins potentially mediating liver damage (TNF-α) have been the main subjects of investigation. In a strictly controlled cohort in Italy (the Dionysus study) heterozygosity for allele C2 of CYP2E1 and homozygosity for allele ADH3*2 of ADH3 were reported to be independent risk factors for ALD in alcohol abusers. Of notice was the observation that in the same Country, two populations with different genetic background leaving only 300 km apart one from the other showed dif-ferent genetic predisposition for ALD. The majority of the genetic data in ALD come from Caucasian and Asian series but Indian populations were seldom investigated. This paper fills this gap, at least partially. Ten different polymorphisms were investigated and associated with or without ALD in 120 subjects from Northern India. Only PNPLA3 allele was associated with ALD but not all the other genes involved in alcohol metabolism, including those reported in Italian series. This apparently inconsistency is not surprising as geographical variations have been reported and are expected. However this discrepancy points for caution in extrapolating results obtained in certain populations to a more general environment. In addition to alcohol intake, several other factors less directly related to the hepatocyte play a role in determining liver damage such as those genes involved in alcohol metabolism, inflammatory pathways and in mesenchymal cell activations. Therefore although assessing the expression of gene(s) may be predictive in certain ethnicity and must be based on preliminary validation studies, this test has to fit in the much more complex puzzle of alcohol intake and liver damage. Considering the complex pathophysiology of ALD, and the ethnically distinct populations, we can conclude that we still have a long way to go.

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