

Examining genetic variations among the Huichol population of Mexico

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Mexican researchers examined the polymorphisms of three enzymes -- alcohol dehydrogenase (ADH1B), aldehyde dehydrogenase (ALDH2) and cytochrome P4502E1 (CYP2E1) -- in the Mestizo and Huichol groups. The Huichols, an indigenous group, had the highest CYP2E1*c2 allele frequency documented in the world. This high frequency, in conjunction with the absence of protective ADH1B and ALDH2 polymorphisms, may place the Huichols at particularly high genetic risk for alcoholism and alcoholic liver disease.

Alcohol abuse is a leading cause of [liver cirrhosis](#) in Mexico. Given that genetics likely play a role in high rates of alcoholic liver disease, researchers analyzed the polymorphisms of [alcohol](#) dehydrogenase (ADH1B), [aldehyde dehydrogenase](#) (ALDH2) and cytochrome P4502E1 (CYP2E1) in two groups in Mexico: the Mestizos, those with mixed genes, and the Huichols, an indigenous group with no racial admixture. Findings show the Huichols have the highest CYP2E1*c2 allele frequency documented in the world to date, placing them at high genetic risk for alcoholism and alcoholic liver disease.

Results will be published in the January 2010 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"The Mexican population is largely the result of indigenous or Amerindian, African and Spanish genes admixture, referred to as Mestizos," explained Blanca Estela Bastidas-Ramírez, a researcher in the

Instituto de Enfermedades Crónico-Degenerativas at the Centro Universitario de Ciencias de la Salud of the University of Guadalajara and corresponding author for the study. "We studied the Huichols because they represent an indigenous group with no racial admixture, and compared them with the Mestizos in order to understand heterogeneity of the Mexican population."

"ADH1B, ALDH2 and CYP2E1 constitute the main alcohol-metabolizing enzymes," explained Hideaki Kato, associate professor in the department of forensic medicine at Nagoya City University Graduate School of Medical Sciences, Japan. "ADH mediates the conversion of alcohol to acetaldehyde, and acetaldehyde is rapidly converted to acetate by ALDH2, and it is eventually metabolized to carbon dioxide and water. Alcohol is also metabolized in smooth endoplasmic reticulum of the liver by the microsomal ethanol oxidizing system, and its major component is CYP2E1."

ADH1B and ALDH2 polymorphisms are said to "protect" from alcoholism because the accumulation of acetaldehyde is very uncomfortable - facial flushing, hypotension, tachycardia, headache, nausea, vomiting - and generally discourages drinking. Conversely, animal experiments have shown that CYP2E1 increases the content of microsomal oxygen and carbonyl free radicals from oxidated ethanol, and these free radicals appear to directly damage the liver cells.

"Orientals are known to carry the 'alcoholism protecting' [genes](#)," added Kato. "However, if individuals carrying the polymorphic alleles keep drinking, they are more likely to develop alcoholic liver diseases caused by acetaldehyde than those who do not, since acetaldehyde is known as a mutagen, a chemical agent that changes the DNA of an organism. The CYP2E1 polymorphism has also been observed in Orientals and, interestingly, in Mexicans, but in Caucasians it is found to a lesser extent."

For this study, Bastidas-Ramírez and her colleagues assessed genotypes and allele frequencies from two groups - 106 Huichols (65 women, 41 men), 20 to 78 years of age, and 331 Mestizos (193 women, 138 men), 31 to 75 years of age - in western Mexico.

"Our key finding is that Huichols exhibit the highest frequency of the CYP2E1*c2 allele compared to anywhere else in the world," said Bastidas-Ramírez.

At the same time, the ADH1B and ALDH2 polymorphisms were practically absent among the Huichols.

Both Bastidas-Ramírez and Kato believe that this "double whammy" - the absence of protective ADH1B and ALDH2 polymorphisms, in conjunction with the highest frequency in the world of damaging CYP2E1*c2 alleles - places the Huichols at extremely high genetic risk for alcoholism and alcoholic liver disease.

"Historical practices and cultural habits have established that the Huichols are used to consuming high amounts of alcohol," said Bastidas-Ramírez. "This high alcohol consumption combined with a high frequency of the CYP2E1*c2 polymorphism may render this population more susceptible to liver cirrhosis and other diseases related to toxic substances activation and oxidative stress. However, it seems that the physical activity, typical nutrition, and total lifestyle of this tribe may also be modulating CYP2E1 expression, but this deserves further study."

Both Bastidas-Ramírez and Kato are excited about the research possibilities.

"The very high CYP2E1*c2 frequency among the Huichols makes this population very interesting for association studies, to understand how the environment can influence gene expression, and to evaluate the

participation of this gene in the development of liver diseases in those indigenous individuals who have been adapted to the Mestizo culture and life style," said Bastidas-Ramírez.

"CYP2E1 is not only an alcohol-metabolizing [enzyme](#), but also plays a central role in the metabolism of many drugs, chemicals and carcinogens," added Kato. "Thus, we would like to know the incidence of cervical, lung, and esophageal cancers in Huichols, which are reported to be associated with CYP2E1 polymorphisms. Furthermore, the high frequency of CYP2E1*c2 alleles in the Huichols is similar to that found in Orientals, supporting the hypothesis that the indigenous population in Mexico have a genetic relationship to Orientals. In contrast, the ADH1B and ALDH2 [polymorphisms](#) in Orientals are high, while they are extremely low in the Huichols. This is also fascinating."

Source: Alcoholism: Clinical & Experimental Research

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