

## LETTER TO THE EDITORS

### INFLUENCE OF GENETIC ADMIXTURE ON POLYMORPHISMS OF ALCOHOL-METABOLIZING ENZYMES: ANALYSES OF MUTATIONS ON THE *CYP2E1*, *ADH2*, *ADH3* AND *ALDH2* GENES IN A MEXICAN–AMERICAN POPULATION LIVING IN THE LOS ANGELES AREA

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(Received 12 June 2002; first review notified 11 July 2002; in revised form 12 August 2002; accepted 1 September 2002)

In pre-Columbian times, the population of Mexico was totally indigenous or Amerindian. When Columbus arrived in the New World, and Cortez marched from Vera Cruz into the Valley of Mexico, a whole new element of genes was introduced into the existing populations. They were a diverse set of genes reflecting Europe and Africa. Today, Mexican–Americans are estimated to be derived from Native Americans by 31%, Spanish by 61%, and African by 8% (Hanis *et al.*, 1991).

Alcohol dehydrogenase 2 (ADH2), alcohol dehydrogenase 3 (ADH3), aldehyde dehydrogenase 2 (ALDH2) and cytochrome P450 2E1 (CYP2E1) are the main alcohol-metabolizing enzymes. These enzyme-encoded genes are polymorphic at several loci and therefore affect enzyme activities. The frequency of gene polymorphisms varies among different ethnic groups. For example, the *ALDH2*\*2 allele, which is responsible for flushing and aversive reactions upon ethanol consumption, is very common in Asians (23–36%) and South American Indians (41–43%) (Goedde *et al.*, 1984; Shen *et al.*, 1997). The frequencies of the *ADH2*\*2 and *ADH3*\*1 alleles, which have been considered to be protective alleles against excessive drinking, are also significantly higher in Asians (70 and 95%, respectively) than Caucasians (4 and 56%, respectively) (Shen *et al.*, 1997). In addition, the *CYP2E1* *RsaI* *c2* allele, which is believed to be associated with increased enzyme activity, is also more common in Asians (17–28%) than in African–Americans and Caucasians (<5%) (Stephens *et al.*, 1994). Despite the higher prevalence of heavy drinking and alcohol-related problems among Mexican–American than other ethnic groups in the USA (Caetano, 1983), few alcohol pharmacogenetic studies in this population have been performed. We therefore examined the genotype of these alcohol-metabolizing enzyme genes in this major minority population residing in Southern California, to determine if Mexican–Americans carry any of those protective alleles against alcohol drinking.

Blood samples were obtained from 251 healthy individuals. They included 105 men (mean age  $\pm$  SD: 32.15  $\pm$  9.17 years) and 146 women (31.90  $\pm$  9.03 years) who had been recruited for previous studies (Wan *et al.*, 1998; Mendoza *et al.*, 2001). All individuals had homogeneous Mexican backgrounds and were defined as having at least three of the four biological parents of the same ethnicity. Genomic DNA was extracted and used for analysing the genetic polymorphisms of *ADH2*, *ADH3*, *ALDH2* and *CYP2E1* by the polymerase-chain reaction followed by restriction enzyme digestion. The distribution and the frequencies of these alleles in this population show a unique ethnic specificity. Mexican–Americans have very low frequencies of the protective *ADH2*\*2 (5%) and *ALDH2*\*2 (0.6%) alleles (Table 1), which are similar to that of Africans and Caucasians. The frequency of the *ADH3*\*1 allele, another protective allele, is also lower in Mexican–Americans (66%) than in Asians (95%). The frequencies for the *RsaI* (*c2*), *DraI* (*C*) and *TaqI* (*A1*) of the *CYP2E1* gene are 14.3, 16.9 and 18.7%, respectively, which are in between the frequencies of Caucasians/African–Americans (1–8%) and Asians (17–28%) (Table 1). The *CYP2E1* *RsaI* *c2* allele frequency is similar between Mexican–Americans and Nicaraguans (Martinez *et al.*, 1998). These data, which contain the largest sample size and a complete allele profile, not only confirm our previous findings (Wan *et al.*, 1998), but also suggest that, without the restraining effects of *ADH2*\*2, *ADH3*\*1 and *ALDH2*\*2, Mexican–Americans may be able to consume large quantities of ethanol. In addition, the presence of the *CYP2E1* *c2* allele may enhance alcohol metabolism. Moreover, the *CYP2E1* genotyping results reflect the fact that Mexican–Americans came from a mixture of two or more population groups that have very different allele frequencies and this genetic mixture might give rise to large interethnic differences at a functional level.

*Acknowledgements* — The work was supported by grants from NIAAA RO1 AA12081 and RO1 AA12081-02S1.

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Table 1. The allele frequencies of *CYP2E1* RsaI c2, *DraI* C, and *TaqI* A1, *ADH2\*2*, *ADH3\*1* and *ALDH2\*2* in different ethnic groups

Ethnic group	<i>CYP2E1</i> RsaI c2(%)	<i>CYP2E1</i> DraI C (%)	<i>CYP2E1</i> TaqI (%)	<i>ADH2*2</i> (%)	<i>ADH3*1</i> (%)	<i>ALDH2*2</i> (%)
Africans	1 <sup>a</sup>	8 <sup>a</sup>	A1	0 <sup>b</sup>		0 <sup>b</sup>
Asians	17–28 <sup>a</sup>	24 <sup>a</sup>		68–71 <sup>c</sup>	92–95 <sup>c</sup>	23–36 <sup>c</sup>
Caucasians	3 <sup>d</sup>	10 <sup>d</sup>	14 <sup>d</sup>	4 <sup>e</sup>	56 <sup>e</sup>	0 <sup>b,f</sup>
South American Indians						41–43 <sup>g</sup>
North American Indians				0 <sup>b</sup>	56 <sup>h</sup>	2–5 <sup>f</sup>
Mexican Indians or Mexicans				3 <sup>i</sup>		0–4 <sup>f,i</sup>
Mexican-Americans in Los Angeles (current study)	14	17	19	5	66	0.6
Nicaraguan	17 <sup>j</sup>					

<sup>a</sup>Stephens *et al.* (1994); <sup>b</sup>Goedde *et al.* (1992); <sup>c</sup>Shen *et al.* (1997); <sup>d</sup>Wong *et al.* (2000); <sup>e</sup>Borras *et al.* (2000); <sup>f</sup>Goedde *et al.* (1986); <sup>g</sup>Goedde *et al.* (1984); <sup>h</sup>Wall *et al.* (1997); <sup>i</sup>Lisker-Yourkowitzky *et al.* (1995); <sup>j</sup>Martinez *et al.* (1998).

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