



Alcoholism and liver disease in Mexico: Genetic and environmental factors

Sonia Roman, Eloy Alfonso Zepeda-Carrillo, Laura Eugenia Moreno-Luna, Arturo Panduro

Sonia Roman, Eloy Alfonso Zepeda-Carrillo, Laura Eugenia Moreno-Luna, Arturo Panduro, Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde" and Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco 44280, Mexico

Eloy Alfonso Zepeda-Carrillo, Universidad Autónoma de Nayarit and Hospital Civil Tepic "Antonio González Guevara", Tepic, Nayarit 63000, Mexico

Author contributions: Roman S and Zepeda-Carrillo EA contributed equally to drafting the manuscript, acquiring the data and critically revising the article; Moreno-Luna LE contributed to acquiring and analyzing the data; Panduro A conceived and drafted the manuscript, analyzed the data and critically revised the manuscript; all of the authors revised and approved the final version.

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Correspondence to: Arturo Panduro, MD, PhD, Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde" and Health Sciences Center, University of Guadalajara, Hospital 278, Col. El Retiro, Guadalajara, Jalisco 44280, Mexico. apanduro@prodigy.net.mx

Telephone: +52-33-36147743 Fax: +52-33-36147743

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Abstract

Alcoholism and cirrhosis, which are two of the most serious health problems worldwide, have a broad spectrum of clinical outcomes. Both diseases are influenced by genetic susceptibility and cultural traits that differ globally but are specific for each population. In contrast to other regions around the world, Mexicans present the highest drinking score and a high mortality rate for alcoholic liver disease with an intermediate category level of per capita alcohol consumption. Mexico has a unique history of alcohol consumption that is linked to profound anthropological and social aspects. The Mexican population has an admixture genome inherited from different races, Caucasian, Amerindian and

African, with a heterogeneous distribution within the country. Thus, genes related to alcohol addiction, such as dopamine receptor D2 in the brain, or liver alcohol-metabolizing enzymes, such as alcohol dehydrogenase class I polypeptide B, cytochrome P450 2E1 and aldehyde dehydrogenase class 2, may vary from one individual to another. Furthermore, they may be inherited as risk or non-risk haplogroups that confer susceptibility or resistance either to alcohol addiction or abusive alcohol consumption and possibly liver disease. Thus, in this era of genomics, personalized medicine will benefit patients if it is directed according to individual or population-based data. Additional association studies will be required to establish novel strategies for the prevention, care and treatment of liver disease in Mexico and worldwide.

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Key words: Alcohol; Genes; Alcoholism; Alcohol dependence; Alcohol addiction; Alcohol abuse; Alcoholic liver cirrhosis; Anthropology

Core tip: Alcoholism and liver disease are leading global health problems. However, the severity and outcome of liver disease appear to vary between individuals and populations. In the present review, we analyze the general scope of alcohol consumption and its relationship with the pattern of drinking score in different countries. We focus on the development of alcoholism in Mexico, which has a strong historical background, and emphasize the need to understand the genetic and environmental factors affecting each population or geographical region of the world.

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INTRODUCTION

The human history of alcohol consumption has been documented for several thousand years^[1]. Alcohol was undoubtedly the result of a fortuitous coincidence that occurred when fruits, grains and flower stalks were fermented for a long time. People may have begun to experience pleasure and happiness after tasting alcoholic beverages^[1,2].

Alcoholic beverages are obtained from different sources, depending on the region of the world. Traditionally, must and wines are produced from grapes of the Middle East and Europe, whisky is made from various grains and sake is obtained from rice in Asia. In Mexico, “pulque” was introduced first, followed by tequila, which are made from the maguey and agave plants, respectively^[3,4].

Historically, alcohol-based beverages have served as a source of needed nutrients and have been widely used for their medicinal, antiseptic and analgesic properties. However, during the last century, alcohol abuse has increased in several countries, thereby augmenting the rate of accidents and liver diseases. The range of liver diseases secondary to alcohol consumption is extensive, including acute alcoholic hepatitis, alcoholic liver disease (ALD), cirrhosis and hepatocellular carcinoma^[5]. Different factors may affect the development of alcoholic liver damage, including the dose, duration and type of alcohol consumption, drinking patterns, gender and ethnicity^[1,6-8]. Other associated risk factors include obesity, iron overload, concomitant viral hepatitis infection^[1,7,9] and genetic factors^[7,8]. Nonetheless, the degree of the association among alcohol consumption, morbidity and mortality due to ALD varies among individuals and populations worldwide. Alcohol consumption and ALD are linked to specific genetic and environmental factors that are prevalent in each population. However, which factors and how they are involved in both alcohol addiction and the adaptation of hepatic genes capable of metabolizing large amounts of ethanol without developing liver disease are challenging questions.

In this comprehensive review, we revisit the information on the worldwide consumption of alcohol and patterns of drinking associated with liver disease, emphasizing the history of alcoholism in Mexico and the differences in the genetic and environmental backgrounds with respect to alcoholism and liver disease among the different countries, with a focus on the genetic factors involved in alcohol dependence and alcohol abuse as well as liver-metabolizing enzymes.

WORLDWIDE ALCOHOL CONSUMPTION

The World Health Organization (WHO) published the total adult per capita alcohol consumption (liters of pure alcohol consumption/year) by distinct geographical

regions of the world^[10]. Three primary categories, high (10-12 L and > 12 L), intermediate (7.5-9.99 L and 5-7.49 L) and low (2.5-4.99 L and < 2.5 L), were created to compare alcohol consumption among different countries.

The countries with the highest alcohol consumption are located primarily in Europe (Czech Republic, United Kingdom, Ireland, Germany, France, Portugal and the Russian Federation) but also in other regions, such as South Korea, Australia, Nigeria, Uganda and Argentina. The intermediate category includes countries located in the Americas, such as the United States, Canada, Mexico, Chile, Brazil and Colombia, a few African countries, such as Cameroon, South Africa, Namibia and Botswana, and Norway in Europe. The low alcohol consumption category includes several countries within the Eastern Mediterranean region and Asia, generally representing those countries where religious beliefs prohibit alcohol consumption.

However, there have been different trends in the last 50 years regarding alcohol consumption in countries worldwide. Although several countries have increased alcohol consumption, others have decreased alcohol consumption (Figure 1). Furthermore, since 2008, the WHO has been in the process of drafting a global strategy to reduce the harmful use of alcohol^[11]. These observations led us to analyze the effectiveness of these strategies to avoid or decrease alcohol consumption and to improve the understanding of the biological and social events involved in the drinking habits of alcohol in Mexico compared with other regions of the world.

MORTALITY DUE TO ALD

To address these concerns, we examined the mortality related to ALD within several countries. Interestingly, there is a discrepancy between mortality related to ALD and the per-capita alcohol consumption^[12]; *e.g.*, Mexico is one of the countries with the highest mortality rate due to ALD but is not included among the countries with the highest alcohol consumption^[12]. However, global comparisons among different populations are limited because not all countries report mortality related to ALD^[12].

PATTERN OF DRINKING SCORE

The pattern of drinking score is a composite scale that ranges from 1 to 5 and focuses primarily on the degree of risk associated with how the alcohol is consumed rather than the amount of alcohol consumed. To build this scale, the following indicators are used: quantity of alcohol consumed by occasion, festive drinking, proportion of drinking events that involve becoming drunk, proportion of drinkers who drink daily, drinking with meals and drinking in public places^[13].

Unlike alcohol consumption, which is measured by the amount of pure alcohol per capita/year, the pattern of drinking score is closely related to ALD. For example, the countries with the highest pattern of drinking score

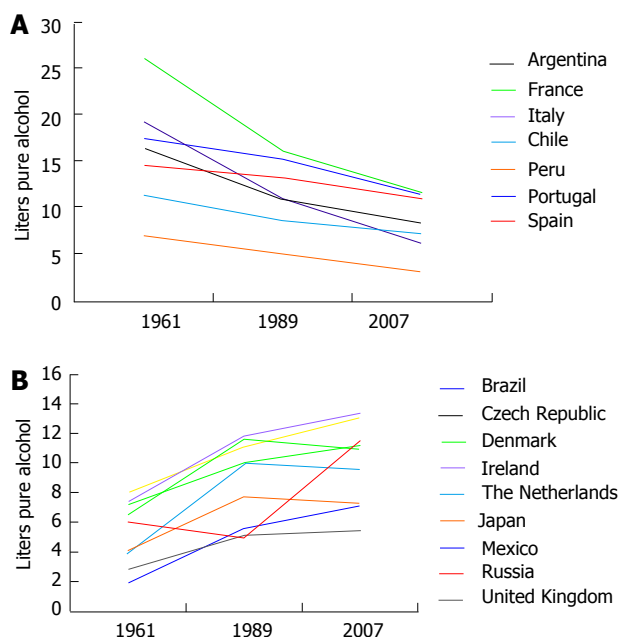


Figure 1 Trends of per-capita alcohol consumption in different countries. A: Countries that decreased consumption per capita since 1961 to 2007; B: Countries that increased consumption per capita since 1961 to 2007.

are Kazakhstan, Mexico, the Russian Federation, South Africa and Ukraine, and the countries with a lower-risk pattern of drinking are Portugal, Spain, France, Italy and Germany^[13].

Taken together, alcohol consumption indicators, mortality rates and pattern of drinking scores, which all may contribute to ALD, are heterogeneous worldwide^[12,13]. Thus, because ALD is a multifactorial problem, researchers should consider the anthropological and historical aspects prevalent among the different societies.

ALCOHOL CONSUMPTION IN MEXICO

Early history of alcohol consumption

To understand the interaction between the evolutionary and genetic changes associated with specific environments, it is necessary to know when and how these events occurred among the different populations. In the case of Mexico, the establishment of a sedentary lifestyle required approximately 5000 years^[14,15]. During this period, the Mesoamericans began the domestication of the well-known staple foods of Mexico, such as maize (*Zea mays* L.), beans (*Phaseolus* spp), squash and pumpkin (*Curcubita* spp) and chili (*Capsicum* spp). This process was accompanied by the discovery and consumption of fermented alcoholic beverages made from a number of endemic agave plants (*Agave* spp). The origin of alcoholic beverages, as described by the Aztecs, was a mythical love story between two deities, “Mayahuel” and “Quetzalcóatl” (Figure 2)^[16-18].

The core of the mature agave plant produces a honey water, or “aguamiel”, rich in amino acids and proteins^[19], which once fermented, produces the traditional alcoholic beverage. The Nahuas in their native language named the



Figure 2 The tale of Mayahuel. The ancient gods gathered in the heavens understood that their people got bored eating only maize and chili; thus, they sent Quetzalcóatl, the god of the winds, to bring the young and beautiful goddess Mayahuel, granddaughter of a “tzintzimitl, a star who attempted to prevent the sun from rising”. Quetzalcóatl and Mayahuel fell in love and together promised that they would give their people a magic plant to recover their happiness. Meanwhile, the evil grandmother noticed that Mayahuel had disappeared; thus, she and other “tzintzimitl” went down to the earth to find her. Mayahuel and Quetzalcóatl were hidden in the form of a tree with two arms (branches); one arm was Mayahuel, and the other was Quetzalcóatl. When the grandmother found them, she cut Mayahuel’s arm into many small pieces, but not Quetzalcóatl’s, who was then transformed into a human again. Nothing could be done for Mayahuel, so Quetzalcóatl buried the leftover pieces in the ground and wept for his loss deeply. Finally, from these parts, the maguey was born. The mature maguey “cries” the honey-water, or “aguamiel”, that emerges from the center of the plant, representing the tears of Quetzalcóatl. “Octli polihuhqui” is the fermented nectar of the maguey that brings happiness. Thus, Mayahuel in the Nahuatl language stands for all that surrounds the maguey^[16,17]. Mayahuel may be considered a dual deity. On the one hand, she represented a woman with many breasts who nourished many children, the 400 rabbits (“Centzon Totochtin”); thus, she was associated with the earth and fertility. On the other hand, she was associated with drunkenness and adultery. This mythological symbol had such great influence that one day of the month was devoted to the rabbit, and those born on that specific date were destined to either be a drunk or commit adultery^[17,18].

former “iztac octli” and the latter “octli polihuhqui”^[20]. However, when the Spaniards arrived on the continent, “octli polihuhqui” was phonetically derived as the term “pulque”^[20,21].

The “octli” but not “octli polihuhqui” served as nourishment for the elderly and sick and for women after childbirth^[22]. The “octli” and perhaps the “octli polihuhqui” were given to all family members, including babies and children, in public ceremonies^[17]. The “octli polihuhqui” was also used for medicinal purposes as an antidepressant or as an anesthetic before human sacrifice^[16,18].

Additionally, the early Mexicans were familiar with the effects of the abuse of “octli polihuhqui”; thus, excessive drinking was strictly prohibited by law primarily during the religious holidays, and a death penalty was implemented^[17]. The Aztec rulers often declared that the abuse of “octli polihuhqui” was the source and beginning of all evil and all ruin^[17]. Unfortunately, these laws were not reinforced after the 15th century, granting a tolerance of the abusive consumption of alcoholic beverages during the colonial period^[4,23].

The rich history of the consumption of “pulque” by the Mexicans over many centuries is an essential compo-

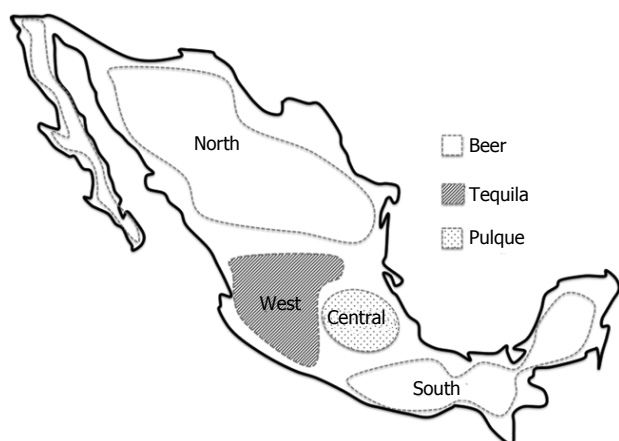


Figure 3 Main types of alcoholic beverages consumed by geographical region in Mexico.

ment of the framework that is required to understand the relationship among the Mexican genome, alcoholism and liver disease at present.

Alcohol consumption in Mexico at present

Mexico is one of the leading countries with a high mortality rate due to liver diseases in the world^[10]. The National Health Secretariat reported an average of 25000 cases of cirrhosis per year from 2000 to 2010^[24]. The primary etiologies of cirrhosis are alcohol, followed by hepatitis C infection and non-alcoholic steatohepatitis^[25-27].

For Mexico, the WHO reported that the amount of alcohol consumed is 8.4 L of pure alcohol per capita among individuals older than 15 years of age, which corresponds to an intermediate category as previously described^[10]. However, if this parameter is applied only to drinkers, alcohol consumption increases to 27.1 L, which is similar to what had been reported in countries with the highest levels of alcohol consumption per capita^[10].

However, the pattern of drinking score shows a better scope of alcoholism among the Mexican population. By examining the amount of alcohol consumed by occasion, we observed that alcohol consumption occurs primarily during the weekends^[28], unlike in Europe where they drink wine almost daily, at lunch or dinner.

Hepatologists may advise their patients not to drink any alcoholic beverage to maintain a healthy liver. However, a large proportion of adults around the world drink alcoholic beverages^[1,5,6]. Thus, the recommendation to avoid liver damage is that the amount of alcohol consumed should be equal or less than 2 drinks per occasion (20-40 g ethanol), not more than 4 drinks per day and not more than 10 to 12 drinks per week, allowing the liver to rest at least 1 or 2 d^[1,5,6]. Furthermore, it has been suggested that the number of alcoholic drinks should be less in women than in men because women have a higher risk for developing ALD^[1,5,6].

However, each weekend, approximately 30 million Mexicans have been estimated to consume more than five drinks per occasion (more than 80 g of ethanol),

with another 10 million consuming at least one alcoholic drink daily. However, alcohol abuse has been detected in 5 million people with a strong dependence on alcohol^[28].

The average Mexican begins consuming alcohol before the age of 18 years perhaps because of a strong cultural influence. Studies conducted in the western region of Mexico have shown that 61.4% of the 12- to 17-year-old have already begun to drink alcohol^[27]. The primary types of alcoholic beverages consumed in Mexico are beer, tequila and “pulque”, and other distilled beverages are consumed in a lower proportion^[27-30]. However, the distribution of alcoholic beverage preferences is heterogeneous. Thus, in central Mexico, “pulque” is preferred, in contrast to tequila in the west or beer in the northern and southern parts of the country (Figure 3). These preferences are associated with the historical cultural background of each region and may be related to the mortality caused by cirrhosis. The mortality rate in central Mexico is greater than 30/100000, followed by the north at less than 10/100000 and the west at less than 5/100000^[30,31].

In western Mexico, young people begin to drink beer either during the weekend or at any social or religious event, such as weddings, coming-of-age parties and christenings. After the initiation of alcohol use, the number of beers consumed per occasion over the weekend ranges from 4 to 6 (80-100 g); this number gradually increases to 20-24 beers/355 mL each (300-360 g of alcohol)/occasion per person over a period of approximately 10 years. The second stage involves the combination of beer with tequila or any other distilled beverage during a period of 8 to 10 years. During this stage, the amount of alcohol consumed ranges from 380 to 640 g daily. In the third stage, alcohol dependence is severe, and patients may or may not present with cirrhosis. By this time, they drink an average of 510 g of alcohol per day (450-720 g)^[26,32-34].

The time between the initiation of alcohol use and the diagnosis of cirrhosis is 23 to 30 years^[26,35]. However, we have identified two distinct age peaks of clinical cirrhosis. In the first group, patients are young, approximately 30 years old, and a plausible genetic predisposition to liver cirrhosis has been proposed to be involved. In the second group, the average age is approximately 45 years^[33]. Compared to other countries, Mexico, according to our findings, may have the youngest people with alcoholic cirrhosis in the world. Apparently, the Apo E2^[33] and FABP2^[36] gene polymorphisms may be involved in the early onset of ALD among the Mexican population.

Clinical profile of Mexican patients with ALD

The majority of patients with ALD seek medical attention in the advanced stages of the disease with a Child-Pugh score of C and multiple complications, such as encephalopathy, variceal bleeding, infections and ascites^[25,27,35]. These clinical characteristics are present in the two primary age groups of patients with alcoholic cirrhosis^[33]. Furthermore, the patients with alcoholic cirrhosis continue to drink high amounts of alcohol after diagnosis

and may die earlier in life due to clinical complications^[25]. This observation may be one of the foremost reasons why hepatocellular carcinoma is rare in Mexico compared with other regions of the world^[37,38], in conjunction with other environmental factors^[39].

ALD has been associated with nutritional deficiencies and malnutrition worldwide^[40]. However, preliminary data from a reference center in western Mexico have shown that obesity is also present. Among 90 patients, 17% of the alcoholic cirrhotic patients were malnourished, whereas overweight and obesity were detected in 33% of the patients, with another 50% of normal weight^[35]. These data are consistent with the fact that Mexico has the highest prevalence of obesity^[41], thus adding a new risk factor for liver disease. Furthermore, in this group of patients, 34% of the patients had drug addictions, which is an increasing social and health problem^[35].

Thus, the combination of alcoholism, obesity, drugs and, in several cases, viral hepatitis B or C, leads us to explore specific strategies for treatments and prevention programs to detect cirrhosis at early stages of the disease.

GENETICS OF ALCOHOL DEPENDENCE OR ALCOHOL ABUSE

In recent decades, researchers have been using various strategies to identify genes that may be associated with alcohol dependence or alcohol abuse. Studies based on candidate genes^[42-45] or linkage disequilibrium were followed by the advances in genotyping that have resulted in the widespread use of genome-wide association studies^[46,47]. Previous studies in families, twins and adoption studies have shown that approximately 40%-60% of the variance in the risk for developing alcoholism can be explained by genetic factors^[43-47]. However, the interactions between genes and several environmental factors have led experts in the field to identify at least two types of alcoholism: (1) a more severe, more genetic and early-onset type of alcoholism; and (2) a less severe, more environmental and late-onset type of alcoholism^[48-52].

Regarding the role of genetic factors in the susceptibility to alcohol dependence and alcohol abuse, research has primarily aimed to study the expression of brain and liver genes. For example, the major brain genes that modulate the neuroadaptive mechanism that translates alcohol stimuli into pleasure, anxiety or cravings are opioid receptor mu 1^[53-55], catechol-*O*-methyltransferase^[56], γ -aminobutyric acid receptor A^[57,58], 5-hydroxytryptamine (serotonin) receptor adenylate cyclase-coupled^[59,60], cholinergic receptor muscarinic 2^[61,62], vesicular monoamine transporter 2^[63-65] and dopamine receptor D2^[48,66-68].

In the liver, several alcohol dehydrogenase (ADH) enzymes, primarily alcohol dehydrogenase class I polypeptide B (ADH1B)^[52], cytochrome P450 2E1 (CYP2E1)^[69] and aldehyde dehydrogenase class 2 (ALDH2)^[52,70], and other minor ADHs, such as ADH1C^[71] and ADH4^[72], have been related to alcohol metabolism and alcoholism. The three major enzyme genes express variants with different

catalytic activities (V_{max}) and Michaelis constants (K_m); thus, their ability to metabolize substrates is variable.

The combination of the allelic profile of these brain and liver genes may affect the risk of or protection against alcohol dependence or alcohol abuse as well as the amount of alcohol metabolized in the liver and the susceptibility to liver damage. Variances in the distribution of these gene polymorphisms may mark phenotypic differences among populations for the aforementioned features. Hence, for this review, the biological functions of dopamine receptor D2 (DRD2), ADH1B, CYP2E1 and ALDH2 are briefly described, and their global allelic frequencies are compared, including those reported for the Mexican population.

DRD2

Alcohol has a stimulatory effect on the dopaminergic neurons of the ventral tegmental area. Dopamine is captured by DRD2 in these neurons in the nucleus accumbens, causing a pleasant effect that is integrated into the mesolimbic system^[48,67,68].

The DRD2 *Taq I A1* polymorphism consists of a T/C nucleotide substitution (rs1800497) that alters the *Taq I* restriction site located 10541 bp downstream of the termination codon. Several studies have investigated the association of this gene polymorphism with alcohol dependence. *Taq I A1* allele carriers reportedly have lower amounts of DRD2 receptors than the *Taq I A2* carriers^[73]. Thus, *A1* allele patients require higher amounts of alcohol to achieve the desired effect^[66-68,74-76]. In additional studies, the association between the *A1* allele *Taq I* and alcohol use disorders has been corroborated in some but not in others. However, in several meta-analyses, a significant association between Caucasian *A1* allele carriers and alcohol addiction has been found^[48,77].

The allelic distribution of DRD2 displays a wide range of frequencies worldwide^[74-79], but the highest prevalence of the *A1* allele is found among the Amerindian Pima (83%) and Mayas (71%) from Mexico^[80,81] (Figure 4).

ADH1B

The *ADH1B* gene has a polymorphic site, resulting in the Arg47His substitution (rs1229984). The *A2* allele (ADH1B His47) confers a 100-fold higher catalytic activity to the ADH1B enzyme than the *A1* allele (ADH1B Arg47). The *A2* allele carriers have a higher ethanol oxidation capacity than the *A1* carriers. However, the *A2* carriers have a higher acetaldehyde production that leads to an alcohol-flushing response that has been considered to be protective.

The protective effect of the *A2* allele against alcohol dependence is well known in the East Asian population^[82]. A study conducted in a cohort of pregnant women from England demonstrated that the *A2* carriers consumed less alcohol before pregnancy, had less incidents of binge drinking during pregnancy and were abstainers during the first trimester of gestation^[83]. However, al-

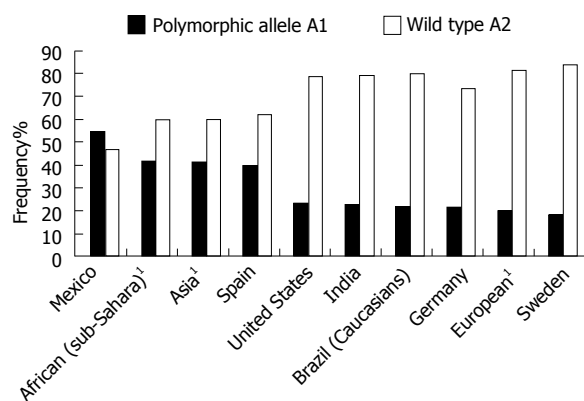


Figure 4 Frequency of Taq I A dopamine receptor D2 polymorphisms in different countries. HapMap.

though this allele apparently reduces the risk of alcohol dependence, it may confer a substantial risk of chronic liver disease, especially among heavy drinkers^[84].

In contrast, *A1* allele carriers do not present with the rapid production of acetaldehyde, which eliminates the alcohol-flushing response. A study conducted in a large cohort of individuals from Copenhagen revealed that *A1* allele homozygotes drank more alcohol and had a higher risk for developing alcohol dependence^[85]. The *A1* allele has also been associated with alcohol dependence in several other studies^[86-88].

CYP2E1

The *CYP2E1* gene, which encodes the enzyme that oxidizes ethanol in the microsomal oxidation system, is essential in the pathophysiology of ALD. Alcohol consumption induces the expression of *CYP2E1*, which is directly involved in the primary oxidation pathway of this substrate, displacing the enzymatic activity of *ADH1B* (K_m : 8-10 mmol/L for *CYP2E1* vs 0.2-2.0 mmol/L for *ADH1B*)^[69,89].

The *C2* allele, which is less common, has a C/T transition at nucleotide position -1019 within the 5' terminal regulatory region. The *C2* allele is associated with a 100-fold higher transcription activity, higher protein concentration and increased enzyme activity, which lead to a faster rate of alcohol oxidation^[90,91].

The *C2* allele carriers have been demonstrated to consume excessive amounts of alcohol, which may be caused by the high transcriptional activity of *CYP2E1*. *C2* allele carriers metabolize ethanol (alcohol) to acetaldehyde at a higher rate. Acetaldehyde is a highly toxic and mutagenic metabolite that increases oxidative stress by producing reactive oxygen species and lipid peroxides, such as 4-hydroxy-2,3-nonenal, 4-hydroxy-2,3-alkenals and malondialdehyde^[92]. An association between an increased risk for ALD and alcoholic cirrhosis has been reported among the carriers of the *C2* allele^[93-95], several of whom belong to the mestizo population of western Mexico^[96].

ALDH2

The *ALDH2* gene encodes the primary mitochondrial

isoform enzyme that oxidizes acetaldehyde to acetate in the liver^[70,97]. The C/G transition in exon 12 of *ALDH2* causes an amino acid substitution of glutamic acid for lysine at position 487 (*ALDH2* Glu487Lys, rs671). The *A2* allele (*ALDH2* Lys487) has little or null enzymatic activity. This deficiency leads to the accumulation of acetaldehyde and consequently provokes a flushing response, which discourages alcohol drinking^[97]. Because flushing is an undesirable symptom, it confers relative protection against abusive alcohol consumption. An association between *A2* allele carriers and a lower risk for alcohol dependence and reduced alcohol use has been reported^[98].

With regard to the distribution of the polymorphisms of the liver alcohol-metabolizing genes, all present contrasting frequencies among different population groups (Figure 5A-C). Among Asians, the *ADH1B* gene displays the highest frequency of the *A2* protective allele, with 78% in Japan and 69% in China. In contrast, the lowest frequency for the *A2* allele was detected in Germany and Mexico, at 4% and 3%, respectively (Figure 5A)^[91,99-105], wherein the frequency of the *A1* allele associated with alcohol dependence was much higher.

The *C2* allele for the *CYP2E1* gene has a frequency of approximately 30% in Japan and China and 2% in the United States. In Chile and Mexico, the frequency is 16% among the mestizo population (Figure 5B)^[91,93,94,105-108]. Interestingly, among the Amerindians of western Mexico, such as the "Huichol" people, this gene polymorphism shows a prevalence of 50%, which is the highest rate reported to date^[91].

The highest frequency of the *A2* allele for the *ALDH* gene has been reported in China (29%) and Japan (26%). In Germany, Sweden and Mexico, its frequency is extremely low or absent^[91,99-105], which could explain, to some extent, the high amount of alcohol consumption that has been reported in those countries.

We could speculate that the selective evolution of both the brain and liver genes was not necessarily directed only by the exposure to alcohol. For example, liver cytochrome genes metabolize a large variety of xenobiotics, whereas those expressed in the brain fulfill the addiction criteria. However, an alternative point of view is to consider these genes as part of a general survival mechanism. Thus, the basic biological necessities of life, such as food (sugars, *e.g.*, glucose) or sexual reproduction, are ensured and rewarded by pleasure; however, these necessities may not be driven by pleasure exclusively.

CONCLUSION

At the end of the last century, we began to understand how liver genes are involved in the metabolism of ethanol and how cerebral genes are related to addictions. Additional genetic studies, including genome-wide association studies, will corroborate the association of specific alleles with alcoholism and ALD. The next step may be a personalized medicine strategy for the prevention, diagnosis and treatment of liver diseases. However, as aforementioned in this review, genes and environmental

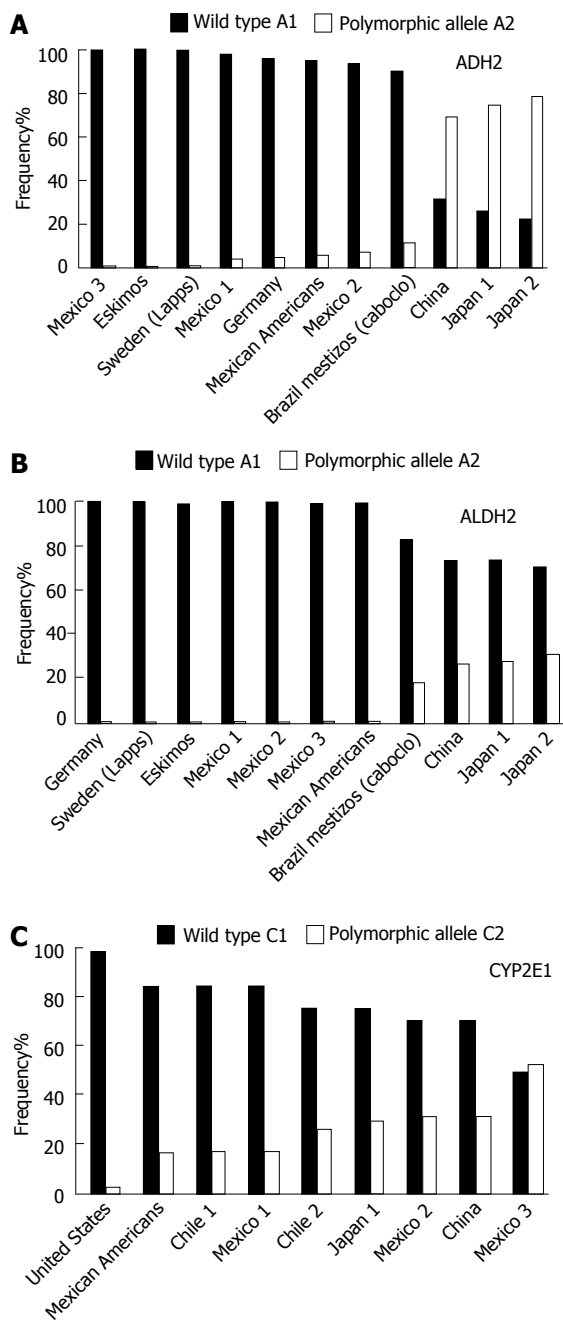


Figure 5 Frequency of polymorphisms of enzymes that metabolize alcohol. A: Alcohol dehydrogenase 2 (ADH2); B: Aldehyde dehydrogenase class 2 (ALDH2); C: Cytochrome P450 2E1 (CYP2E1) in different countries. A-B: Mexico 1: Western Mexico; Mexico 2: Native from Mexico "Otomi"; Mexico 3: Native from Mexico "Huicholes"; Japan 1: Rural country; Japan 2: Mestizos from Japan; C: Mexico 1: Western Mexico; Mexico 2: North an central Mexico; Mexico 3: Native from Mexico "Huicholes"; Chile 1: Mestizos; Chile 2: Native from Chile "Mapuches".

factors are involved in the development of ALD, which requires an in-depth analysis of the different populations. Therefore, the data found in several regions of the world may not correlate to populations from different geographic areas.

Mexicans are an admixture population that has inherited specific alleles from different races, predominantly Caucasian, Amerindian and African^[109,110]. Based on the

current data on allelic frequencies in different countries, the Mexican population has a particular genetic profile that may explain the epidemiological and clinical manifestations of alcohol-related liver diseases. Thus, the expectation that the different allelic variants of the aforementioned genes (*DRD2*, *ADH2*, *CYP2E1* and *ALDH2*) will express themselves individually is plausible. However, considering these alleles as a haplogroup may generate risk or non-risk phenotypes related to liver disease, as well as to proneness towards or resistance against the high intake of alcohol. Haplogroups that could confer a non-risk phenotype for alcoholism and liver damage could be *DRD2*A2*, *ADH2*A2*, *CYP2E1*C1*, *ALDH2*A2* and *DRD2*A2*, *ADH2*A1*, *CYP2E1*C1*, *ALDH2*A2* because they are related to non-addiction plus flushing by the accumulation of acetaldehyde, exhibiting a protective effect. The haplogroups that could confer risk phenotypes for alcoholism and liver damage could be *DRD2*A1*, *ADH2*A1*, *CYP2E1*C1*, *ALDH2*A1* and *DRD2*A1*, *ADH2*A1*, *CYP2E1*C2*, *ALDH2*A1* because these are related to addiction plus the efficient metabolism of alcohol but exposure to acetaldehyde. This observation may explain why some patients who consume heavy amounts of alcohol per day (> 80 g/d) for more than 20 years do not have liver damage, whereas others with a less than or equal to consumption level and less exposure suffer liver damage and even die from cirrhosis or its complications^[1,6,7]. However, additional studies are required to demonstrate the association between these hypothetical allelic profiles and the clinical outcomes of alcohol-dependent patients in Mexico and worldwide.

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