Association of a novel *TAS2R38* haplotype with alcohol intake among Mexican-Mestizo population

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ABSTRACT

Background. Alcohol intake has been associated with the bitter taste receptor T2R38. *TAS2R38* gene expresses two common haplotypes: PAV and AVI. It has been reported that AVI homozygotes consume more alcohol than heterozygotes and PAV homozygotes. The aim of this study was to determine the prevalence of the *TAS2R38* haplotypes among Mexican-Mestizo population and to analyze its association with alcohol intake. **Material and methods.** In a cross-sectional study, a total of 375 unrelated Mestizo individuals were genotyped for *TAS2R38* polymorphisms (A49P, V262A and I296V) by a Real-Time PCR System (TaqMan). Haplotype frequencies were calculated. Association of *TAS2R38* haplotypes with alcohol intake was estimated in drinkers (DRS) and nondrinkers (NDRS). **Results.** Two haplotypes accounted for over 96% of all haplotypes (AVV, 60%, and PAI, 36.5%). The frequency of AVV homozygotes was significantly higher in DRS than NDRS (47.2 *vs.* 32.2%, respectively; $p < 0.05$). Additionally, the AVV/AVV genotype was associated with alcohol intake when compared with heterozygotes and PAI homozygotes (OR = 1.79, 95% CI 1.13-2.84, $p < 0.05$ and OR = 2.23, 95% CI 1.11-4.48; $p < 0.05$, respectively). **Conclusions.** In conclusion, two *TAS2R38* haplotypes (AVV and PAI) prevailed in Mexican-Mestizo population. The novel AVV haplotype was associated with alcohol intake. The high prevalence of this allelic profile in our population could help to explain, at least in part, the preference for alcohol among the Mexicans.

Key words. Bitter taste. Bitter taste perception. *TAS2R38* haplotypes. Alcohol intake, Mexico.

INTRODUCTION

Bitter taste perception is considered an important dietary adaptation,[1-3] which is associated with the intake of bitter-tasting foods such as cruciferous vegetables, sharp cheeses, soy products, grapefruit, green tea and coffee.[4] However, it has been reported that ethanol (alcohol) also elicits a bitter taste in humans.[5,6] Based on the response to the synthetic thiourea bitter-tasting compounds phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP), individuals can be classified as tasters or nontasters

as they perceive more and less intensely bitter taste, respectively.[7,8] However, the proportion of both PTC/PROP phenotypes varies among different populations worldwide.[9] Scientific evidence support that bitter taste perception is mediated by the Taste 2 Receptors (TAS2R), a family of G protein-coupled taste receptors encoded by almost 25 functional TAS2R genes.[10] In particular, *TAS2R38* has been identified as the gene for PTC sensitivity, which is located on chromosome 7.[11]

Three single nucleotide polymorphisms (SNPs) within the *TAS2R38* gene which encode for amino acid substitutions at position 49 (alanine/proline, A49P), 262 (valine/alanine, V262A) and 296 (isoleucine/valine, I296V) may explain up to 85% of the observed variance in PTC taste sensitivity. Recently, it was demonstrated that alcohol bitterness depends upon the expression of these three *TAS2R38* SNPs,[12] which may explain the variability in the preference for alcoholic beverages.[13-15] Moreover, several *TAS2R38* haplotypes corresponding to the amino acids at the three positions have been re-

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ported, being PAV and AVI the most common.[16] PAV and AVI homozygotes exhibit the highest and lowest bitter taste sensitivity, respectively while PAV/AVI heterozygotes show an intermediate phenotype.[17] Consistent with this, several studies have shown that AVI homozygotes consume more alcohol than heterozygotes and PAV homozygotes.[18-20] Interestingly, greater bitterness perception may not necessarily induce alcohol rejection since studies have shown that wine expertise can be predicted by the PROP tasting phenotype.[21]

Mexico is currently one of the leading countries with the highest drinking score and a high mortality rate for alcoholic liver disease. Consequently, the comprehensive analysis of the genetic and environmental factors involved in alcohol intake, including those related to bitter taste perception may help to explain the high alcohol consumption of modern-day admixture Mexicans.[22] Therefore, the aim of this study was to determine the prevalence of the *TAS2R38* haplotypes among Mexican-Mestizo population and to analyze its association with alcohol intake.

MATERIAL AND METHODS

Study population

In a cross-sectional study, a total of 375 unrelated Mestizo individuals from the city of Guadalajara (GDL) in the state of Jalisco were analyzed. The subjects were classified according to the recommendations of alcohol intake to prevent liver damage as drinkers (DRS) and nondrinkers (NDRS).[23,24] A medical history questionnaire was designed to register the amount of alcohol intake, which was expressed as:

g ethanol = volume mL x % alcohol x 0.8/100.

The following amounts were considered:

• 1 shot of tequila = 35 mL (11.2 g ethanol).
• 1 beer = 330 mL (12.3 g ethanol).
• 1 glass of red wine = 120 mL (14.4 g ethanol).

Based on the pattern of alcohol consumption in West Mexico, DRS consumed more than two drinks per occasion, while NDRS consumed equal or less than two drinks per occasion.[22] Smokers and subjects who had chronic sinus problems or who had any prescribed medication that might affect taste perception were excluded.

TAS2R38 genotyping

DNA was extracted from leucocytes by a modified salting-out method.[25] *TAS2R38* genotyping was performed by a Real-Time PCR System (TaqMan, Applied Biosystems, assay numbers C_9506826, C_9506827, and C_8876467; Foster City, CA) on a 96-well format and read by a Step One Plus (Applied Biosystems, Foster City, CA). DNA was used at a final concentration of 70 ng. Conditions of the polymerase chain reaction were 95 °C for 10 min and 40 cycles of denaturation at 92 °C for 15 s and annealing/extension at 60 °C, for 1 min. Genotyping was verified by using positive controls of the DNA samples corresponding to the three possible genotypes in each 96-well plate as well as rerunning 25% of the samples, which were 100% concordant.

Anthropometric measurements

Height measurement was determined by using a clinical scale with a stadiometer (Rochester Clinical Research, New York, USA) during the patient's visit. Electrical bioimpedance determined body mass index (BMI, kg/m^2) with an INBODY 3.0 analyzer (Analyzer Body Composition, Biospace, Korea).

Biochemical tests

Ten mL blood samples were drawn by venipuncture after a 12-h fast and separated into two aliquots; one for DNA isolation and another for determination of biochemical tests that included glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transferase (GGT), total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-c). Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula,[26] and very low-density lipoprotein cholesterol (VLDL-c) concentration was calculated as Total Cholesterol - (LDL-c + HDL-c). Dry chemistry determined all biochemical tests on a Vitros 250 Analyzer (Ortho Clinical Diagnostics, Johnson & Johnson Co, Rochester, NY). For quality control purposes, we used a pooled human serum and a commercial control serum (Ortho Clinical Diagnostics, Johnson & Johnson Co) to account for imprecision and the inaccuracy of the biochemical measurements. The intra-assay variability (CV%) of biochemical assays was relative to ten repeated determinations of the control serum in the same analytical session, whereas inter-assay CV% for each variable was calculated on the mean values

Table 1. Allelic and genotypic frequencies of the *TAS2R38* polymorphisms (A49P, V262A and I296V).

SNPs	n	HWE	LD	Alleles n (%)		Genotypes n (%)		
				A	P	A/A	A/P	P/P
A49P	375	0.84	<0.001	229.5 (61.2)	145.5 (38.8)	139.5 (37.2)	180 (48)	55.5 (14.8)
				V	A	V/V	V/A	A/A
V262A	375	0.84	<0.001	236 (62.9)	139 (37.1)	147 (39.2)	178 (47.4)	50 (13.4)
				I	V	I/I	I/V	V/V
I296V	375	0.55	<0.001	142 (37.9)	233 (62.1)	51 (13.7)	182 (48.5)	142 (37.9)

N: number. HWE: Hardy Weinberg Equilibrium. LD: Linkage Disequilibrium. HWE and LD data are reported as p-value of chi-square test. Allelic and genotype frequencies are expressed as percentage.

of control serum measured in five analytical sessions. When necessary, the serum was diluted with bovine serum albumin according to the manufacturers' instructions.

Statistical analyses

Statistical differences between experimental groups for quantitative and qualitative variables were analyzed by *t*-student and Chi-square test, respectively with the SPSS software (version 20). Hardy-Weinberg equilibrium (HWE) and linkage disequilibrium (LD) as well as haplotype frequencies were obtained by using Arlequin software (version 3.1). To analyze the association of *TAS2R38* haplotypes with alcohol intake an odds ratio test (OR) was performed in the Epi-info [TM]7 software (CDC, Atlanta, GA). A p-value < 0.05 was considered significant.

Ethical guidelines

The study protocol complied with the ethical guideline for the 2013 Declaration of Helsinki and was approved by the local Hospital Ethical Committee. All participants filled out a written informed consent.

RESULTS

Allelic and genotype frequencies of the *TAS2R38* polymorphisms (A49P, V262A and I296V) are shown in Table 1. The distribution of genotypes was concordant with the HWE. Additionally, the three genetic variants were in strong LD (p < 0.001). Two haplotypes accounted for over 96% of all haplotypes (AVV, 60%, and PAI, 36.5%) whereas the remaining four haplotypes were rare (PVV, 2%) or extremely rare (AVI, < 1%, AAI, < 1%, and PVI, < 1%). Of the most frequent haplotypes, 36% were AVV homozygotes, 45.1% heterozygotes and 12.8% PAI homozygotes. Demographic and biochemical characteristics of DRS and NDRS are shown in Table 2. No differences for the variables of age, BMI, TC, HDL-c and VLDL-c were found. By contrast, DRS had a higher proportion of men and higher levels of glucose, TG, LDL-c, ALT, AST and GGT than NDRS. The frequency of AVV homozygotes was significantly higher in DRS than NDRS (47.2 *vs.* 32.2%, respectively; p < 0.05) (Figure 1) and this genotype was associated with alcohol intake when compared with heterozygotes and PAI homozygotes (OR = 1.79, CI 1.13-2.84, p < 0.05 and OR = 2.23, CI 1.11-4.48; p < 0.05, respectively).

DISCUSSION

Globally, the most common *TAS2R38* haplotypes are AVI and PAV.[16] However, in this study, the AVV and PAI haplotypes were the most predominant among the study population. Although the PAI haplotype has been identified in other populations, its frequency was extremely low.[27] In contrast, the AVV haplotype found in this study has not been reported elsewhere to date. Its high frequency may be due to the unexpected dominance of the valine variant at position 296 distributed among the I/V-V/V genotypes. Functional expression studies demonstrate that the presence of alanine at position 49 and valine at position 262 diminishes receptor function, whereas the variation in position 296 had little effect.[28] Notably, the AVI and AVV haplotypes have the same effect of not responding to the bitter taste compounds PTC/PROP (non tasters), whereas the PAV and PAI variants respond equally strong (tasters).

Table 2. Demographic and biochemical characteristics of NDRS and DRS.

Variable	NDRS	DRS	p-value
Subjects participants (n)	220	155	-
Age (years)	37.7 ± 13.4	40.6 ± 13.8	NS
Gender (F/M) (n)	(161 / 59)	(21 / 134)	< 0.001
BMI (kg/m^2)	28.9 ± 5.8	28 ± 5.2	NS
Glucose (mg/dL)	92.2 ± 18.1	103.1 ± 59	< 0.05
TC (mg/dL)	194.1 ± 45.8	188.2 ± 58.2	NS
TG (mg/dL)	165.6 ± 168.8	202 ± 134.2	< 0.05
HDL-c (mg/dL)	43.6 ± 16.5	39.8 ± 17.1	NS
LDL-c (mg/dL)	122 ± 37.2	111.6 ± 48.1	< 0.05
VLDL-c (mg/dL)	33.6 ± 34.6	39.1 ± 25	NS
ALT (IU/L)	29.1 ± 19.5	35.8 ± 29.6	< 0.05
AST (IU/L)	27.9 ± 13.6	43.2 ± 40.7	< 0.001
GGT (IU/L)	31.1 ± 74.5	85.6 ± 146.9	< 0.001

Average values are expressed as mean ± SD. DRS: drinkers. NDRS: non drinkers. BMI: body mass index. TC: total cholesterol. TG: triglycerides. HDL-c: high density lipoprotein cholesterol. LDL-c: low density lipoprotein cholesterol. VLDL-c: very low density lipoprotein cholesterol. ALT: alanine aminotransferase. AST: aspartate aminotransferase. GGT: gamma-glutamyl-transferase. NS: not significant. n: number.
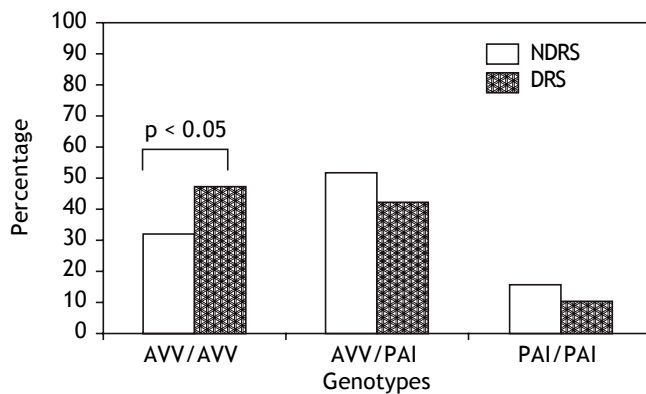

Figure 1. Frequencies of the TAS2R38 *genotypes among DRS and NDRS. DRS: drinkers. NDRS: non drinkers.*

In this study, we also demonstrated that the frequency of the AVV homozygotes was higher in DRS than NDRS and this genotype was associated with alcohol intake when compared with heterozygotes and PAI homozygotes. These findings are consistent with other reports evaluating the effect of the *TAS2R38* haplotypes with alcohol intake,[18-20] and may be explained because decreased receptor function by AVV haplotype causes an increase in taste perception thresholds, which ultimately leads to the consumption of a greater amount of alcohol. Moreover, although it has been reported that gender influences alcohol intake,[29] in this study male gender was not a confounder factor despite the high amount of men in the drinkers group because it was not related to alcohol intake matched by *TAS2R38* haplotype.

In regards to the bitter taste phenotype and alcoholism relationship, some studies have reported an association between alcoholism and PROP tasting ability,[30,31] while other studies have not found such association.[32-34] However, these discrepancies may be caused by methodological flaws in sample size, tasting classification, drinking habits and the effect of other tastes.

In Mexico, the alcoholic beverage preferences are heterogeneous. For instance, tequila is the main beverage consumed in West Mexico; while "pulque" and "mezcal" are preferred in the central region, in contrast to beer in the northern and southern parts of the country.[21] Thereby, further studies are needed to elucidate the relation between the taste of these beverages and its consumption. In addition to bitter taste, the role of other tastes in alcohol intake has been analyzed. For example, it was reported that subjects who are at risk of alcoholism by having an alcoholic father, rated salty and sour solutions as more unpleasant than those with no such paternal history.[35,36] Moreover, several studies suggest that sweet-liking is also associated with a paternal history of alcohol dependence.[37-40]

Because excessive and chronic alcohol consumption are inherent features required to reach alcoholism, *TAS2R38* may be a promising candidate gene for alcoholic dependence.[41] However, no evidence has been found that *TAS2R38* haplotypes influence alcohol dependence in high-risk women of African-American origin.[19] Thus, population-specific features are modulated by genetic and environmental factors affecting alcohol intake that require further

investigation.[21,42] For instance, specific alleles such as the dopamine receptor *DRD2*A1,* the alcohol-metabolizing enzymes *ADH2*A1, CYP2E1*C1* and *ALDH2**A1 and the transporter proteins involved in lipid metabolism *APOE*2* and *FABP2**Thr54 have been associated with alcoholism and chronic liver disease in the Mexican population.[43-46] However, these findings may differ with those reported in other populations worldwide.

CONCLUSION

In conclusion, two *TAS2R38* haplotypes (AVV and PAI) prevailed in Mexican-Mestizo population. The novel AVV haplotype was associated with alcohol intake. The high prevalence of this allelic profile in our population could help to explain, at least in part, the preference for alcohol among the Mexicans.

REFERENCES

1. Tepper BJ. 6-n-Propylthiouracil: a genetic marker for taste, with implications for food preference and dietary habits. *Am J Hum Genet* 1998; 63: 1271-6.
2. Campbell MC, Thishkoff SA. The evolution of human genetic and phenotypic variation in Africa. *Curr Biol* 2010; 20: R166-73.
3. Campbell MC, Ranciaro A, Froment A, Hirbo J, Omar S, Bodo JM, Nyambo T, et al. Evolution of functionally diverse alleles associated with PTC bitter taste sensitivity in Africa. *Mol Biol Evol* 2012; 29: 1141-53.
4. Garcia-Bailo B, Toguri C, Eny KM, El-Sohemy A. Genetic variation in taste and its influence on food selection. *OMICS* 2009; 13: 69-80.
5. Noble AC. Bitterness in wine. *Physiol Behav* 1994; 56: 1251-5.
6. Scinska A, Koros E, Habrat B, Kukwa A, Kostowski W, Bienkowski P. Bitter and sweet components of ethanol taste in humans. *Drug Alcohol Depend* 2000; 60: 199-206.
7. Kim UK, Drayna D. Genetics of individual differences in bitter taste perception: lessons from the PTC gene. *Clin Genet* 2005; 67: 275-80.
8. El-Sohemy A, Stewart L, Khataan N, Fontaine-Bisson B, Kwong P, Ozsungur S, Cornelis MC. Nutrigenomics of taste - impact on food preferences and food production. *Forum Nutr* 2007; 60: 176-82.
9. Guo SW, Reed DR. The genetics of phenylthiocarbamide perception. *Ann Hum Biol* 2001; 28: 111-42.
10. Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER. Genetic variation in taste perception: does it have a role in healthy eating? *Proc Nutr Soc* 2011; 70: 135-43.
11. Tepper BJ. Nutritional implications of genetic taste variation: the role of PROP sensitivity and other taste phenotypes. *Annu Rev Nutr* 2008; 28: 367-88.
12. Allen AL, McGeary JE, Hayes JE. Polymorphisms in TRPV1 and TAS2Rs associate with sensations from sampled ethanol. *Alcohol Clin Exp Res* 2014; 38: 2550-60.
13. Tepper BJ, White EA, Koelliker Y, Lanzara C, d'Adamo P, Gasparini P. Genetic variation in taste sensitivity to 6-n-propylthiouracil and its relationship to taste perception and food selection. *Ann N Y Acad Sci* 2009; 1170: 126-39.
14. Hayes JE, Feeney EL, Allen AL. Do polymorphisms in chemosensory genes matter for human ingestive behavior? *Food Qual Prefer* 2013; 30: 202-16.
15. Ramos-Lopez O, Ojeda-Granados C, Roman S, Panduro A. Influencia genética en las preferencias alimentarias. *Rev Endocrinol Nutr* 2013; 21: 74-83.
16. Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 2003; 299: 1221-5.
17. Drayna D. Human taste genetics. *Annu Rev Genomics Hum Genet* 2005; 6: 217-35.
18. Duffy B, Davidson AC, Kidd JR, Kidd KK, Speed WC, Pakstis AJ, Reed DR, et al. Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. *Alcohol Clin Exp Res* 2004; 28: 1629-37.
19. Wang JC, Hinrichs AL, Bertelsen S, Stock H, Budde JP, Dick DM, Bucholz KK, et al. Functional variants in TAS2R38 and TAS2R16 influence alcohol consumption in high-risk families of African-American origin. *Alcohol Clin Exp Res* 2007; 31: 209-15.
20. Hayes JE, Wallace MR, Knopik VS, Herbstman DM, Bastoshuk LM, Duffy VB. Allelic variation in TAS2R bitter receptor genes associates with variation in sensations from and ingestive behaviors toward common bitter beverages in adults. *Chem Senses* 2011; 36: 311-9.
21. Hayes JE, Pickering GJ. Wine Expertise Predicts Taste Phenotype. *Am J Enol Vitic* 2012; 63: 80-4.
22. Roman S, Zepeda-Carrillo EA, Moreno-Luna LE, Panduro A. Alcoholism and liver disease in Mexico: genetic and environmental factors. *World J Gastroenterol* 2013; 19: 7972-82.
23. O'Shea RS, Dasarathy S, McCullough AJ; Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. *Hepatology* 2010; 51: 307-28.
24. Cainelli F. Liver diseases in developing countries. *World J Hepatol* 2012; 4: 66-7.
25. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res* 1988; 16: 1215.
26. Tremblay AJ, Morrissette H, Gagné JM, Bergeron J, Gagné C, Couture P. Validation of the Friedewald formula for the determination of low-density lipoprotein cholesterol compared with beta-quantification in a large population. *Clin Biochem* 2004; 37: 785-90.
27. Mennella JA, Pepino MY, Duke FF, Reed DR. Age modifies the genotype-phenotype relationship for the bitter receptor TAS2R38. *BMC Genet* 2010; 11: 60.
28. Bufe B, Breslin PA, Kuhn C, Reed DR, Tharp CD, Slack JP, Kim UK, et al. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. *Curr Biol* 2005; 15: 322-7.
29. Kampov-Polevoy AB, Eick C, Boland G, Khalitov E, Crews FT. Sweet liking, novelty seeking, and gender predict alcoholic status. *Alcohol Clin Exp Res* 2004; 28: 1291-8.
30. Pelchat ML, Danowski S. A possible genetic association between PROP-tasting and alcoholism. *Physiol Behav* 1992; 51: 1261-6.
31. DiCarlo ST, Powers AS. Propylthiouracil tasting as a possible genetic association marker for two types of alcoholism. *Physiol Behav* 1998; 64: 147-52.
32. Intranuovo LR, Powers AS. The perceived bitterness of beer and 6-n-propylthiouracil (PROP) taste sensitivity. *Ann N Y Acad Sci* 1998; 855: 813-5.

33. Kranzler HR, Moore PJ, Hesselbrock VM. No associa-tion of PROP taster status and paternal history of al-cohol dependence. *Alcohol Clin Exp Res* 1996; 20: 1496-500.
34. Kranzler HR, Skipsey K, Modesto-Lowe V. PROP taster sta-tus and parental history of alcohol dependence. *Drug Al-cohol Depend* 1998; 52: 109-13.
35. Scinska A, Bogucka-Bonikowska A, Koros E, Polanowska E, Habrat B, Kukwa A, Kostowski W, et al. Taste re-sponses in sons of male alcoholics. *Alcohol Alcohol* 2001; 36: 79-84.
36. Sandstrom KA, Rajan TM, Feinn R, Kranzler HR. Salty and sour taste characteristics and risk of alcoholism. *Alcohol Clin Exp Res* 2003; 27: 955-61.
37. Kampov-Polevoy AB, Tsoi MV, Zvartau EE, Neznanov NG, Khalitov E. Sweet liking and family history of alcoholism in hospitalized alcoholic and non-alcoholic patients. *Alcohol Alcohol* 2001; 36: 165-70.
38. Kampov-Polevoy AB, Garbutt JC, Khalitov E. Family history of alcoholism and response to sweets. *Alcohol Clin Exp Res* 2003; 27: 1743-9.
39. Kampov-Polevoy AB, Ziedonis D, Steinberg ML, Pinsky I, Krejci J, Eick C, Boland G, et al. Association between sweet preference and paternal history of alcoholism in psychiatric and substance abuse patients. *Alcohol Clin Exp Res* 2003; 27: 1929-36.
40. Wronski M, Skrok-Wolska D, Samochowiec J, Ziolkowski M, Swiecicki L, Bienkowski P, Korkosz A, et al. Perceived in-tensity and pleasantness of sucrose taste in male alcohol-ics. *Alcohol Alcohol* 2007; 42: 75-9.
41. Mustavich LF, Miller P, Kidd KK, Zhao H. Using a pharmacoki-netic model to relate and individual's susceptibility to alcohol dependence to genotypes. *Hum Hered* 2010; 70: 177-93.
42. Machado IE, Lana FC, Felisbino, Mendes MS, Malta DC. Factors associated with alcohol intake and alcohol abuse among women in Belo Horizonte, Minas Gerais State, Bra-zil. *Cad Saude Publica* 2013; 29: 1449-59.
43. Salguero ML, Leon RE, Santos A, Roman S, Segura-Ortega JE, Panduro A. The role of FABP2 gene polymorphism in al-coholic cirrhosis. *Hepatol Res* 2005; 33: 306-12.
44. Hernández-Nazará ZH, Ruiz-Madrigal B, Martínez-López E, Roman S, Panduro A. Association of the epsilon 2 allele of APOE gene to hypertriglyceridemia and to early-onset al-coholic cirrhosis. *Alcohol Clin Exp Res* 2008; 32: 559-66.
45. Gordillo-Bastidas E, Panduro A, Gordillo-Bastidas D, Zepeda-Carrillo EA, García-Bañuelos JJ, Muñoz-Valle JF, Bastidas-Ramírez BE. Polymorphisms of alcohol metabolizing enzymes in indigenous Mexican population: unusual high frequency of CYP2E1*c2 allele. *Alcohol Clin Exp Res* 2010; 34: 142-9.
46. García-Bañuelos J, Panduro A, Gordillo-Bastidas D, Gor-dillo-Bastidas E, Muñoz-Valle JF, Gurrola-Díaz CM, Sánchez-Enríquez S, et al. Genetic polymorphisms of genes coding to alcohol-metabolizing enzymes in west-ern Mexicans: association of CYP2E1*c2/CYP2E1*5B al-lele with cirrhosis and liver function. *Alcohol Clin Exp Res* 2012; 36: 425-31.