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Original Article

C3435T polymorphism in the *MDR1* gene and breast cancer risk in northeastern Mexico

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Abstract: The multidrug resistance gene 1 (*MDR1*) encodes a membrane-bound phosphoglycoprotein (P-gp). It functions as a transmembrane efflux pump for various structurally unrelated carcinogens and toxins. Polymorphism C3435T of *MDR1* has been investigated for its association with breast cancer in different populations. However, the results are inconsistent and inconclusive. The objective of this study was to determine whether an association exists between the *MDR1* C3435T polymorphism and the risk of breast cancer in a population from northeastern Mexico, which displays ethnic characteristics that differentiate it from other populations of the country. Genotypes were determined for 243 women with histologically confirmed breast cancer and 118 control subjects. Polymorphism of *MDR1* C3435T was analyzed by DNA microarray. We found an increased breast cancer risk associated with CT and CC genotypes (OR = 1.88, 95% CI: 1.04-3.39, P = 0.033 for CT vs. TT; OR = 2.91, 95% CI: 1.48-5.74, P = 0.001 for CC vs. TT). Furthermore, there was significantly increased risk of breast cancer associated with the C allele (OR = 1.59, 95% CI: 1.16-2.18, P = 0.003). In conclusion, we found an association between the *MDR1* C3435T polymorphism and risk of breast cancer in subjects from northeastern Mexico. Identification of inter-individual variability in this polymorphism may be useful for individualizing breast cancer genetic screening and therapeutic intervention.

Keywords: Breast cancer, multidrug resistance gene 1 (*MDR1*), *MDR1* C3435T polymorphism, ethnicity, Mexico

Introduction

Breast cancer is the most common type of cancer and the most common cause of cancer death among women worldwide [1]. The disease has important genetic and environmental factors, most of them still unknown. It is possible that the mechanism of breast carcinogenesis may representa complex interplay between exposure to potential toxins and carcinogens and the genes involved in the detoxification pathways [2].

The multidrug resistance gene 1 (*MDR1*) encodes a membrane-bound phosphoglycoprotein (P-gp). It functions as a transmembrane efflux pump for various structurally unrelated carcinogens and toxins such as organic cations, amino acids, polysaccharides, proteins, and antibiotics [3, 4].

MDR1 is highly polymorphic with more than 50 single-nucleotide polymorphisms (SNPs) identified [5]. One of the most important SNPs is C3435T in exon 26, which alters gene expression, protein activity, and substrate specificity. It may limit the local detoxification activity in breast tissue and be a risk factor for cancer development and behavior [6-8]. Several studies have investigated the relationship between the C3435T polymorphism and the risk of breast cancer in different populations. However, the findings of these studies are still inconclusive [8-19, see also meta-analyses 20-25].

In Mexico, two related studies have been carried out, in which only subjects from the central-western area of the country were analyzed [26, 27]. We previously investigated the relationship between several genetic polymorphisms and breast cancer in northeastern Mexico and found significant differences with other populations of the country [28, 29]. The purpose of this study was to determine whether an association exists between the *MDR1* C3435T

Table 1. Genotype and allele frequencies of the C3435T polymorphism of the multidrug resistance gene 1 (*MDR1*) in breast cancer patients and healthy controls from northeastern Mexico

Variable	Cases* (%)	Controls (%)	OR (95% CI)	P
Genotypes				
TT	31 (13.0)	29 (24.6)	Reference	
CT	129 (54.2)	64 (54.2)	1.88 (1.04-3.39)	0.033
CC	78 (32.8)	25 (21.2)	2.91 (1.48-5.74)	0.001
Alleles				
T	95 (40.0)	61 (52.0)	Reference	
C	143 (60.0)	57 (48.0)	1.59 (1.16-2.18)	0.003

*Numbers may not sum to total due to missing data. OR-odds ratio; CI-confidence interval.

polymorphism and the risk of breast cancer in subjects from northeastern Mexico.

Material and methods

Study population

The subjects and methods have been described in detail in previous reports [28-30]. The case subjects were 243 women with histologically confirmed breast cancer treated at the University Cancer Center of the University Hospital "Dr José E González" of the Autonomous University of Nuevo Leon and the Hospital of Specialties number 25 of the Mexican Institute of Social Security, both located in Monterrey, Nuevo Leon, Mexico. Both are reference centers for breast cancer patients from throughout the northeastern area of Mexico, which includes the states of Coahuila, Nuevo Leon, San Luis Potosi, Tamaulipas, and Zacatecas. One hundred eighteen controls with no previous history of any type of cancer or other vital disease were also studied. The study was performed in accordance with the tenets of the Declaration of Helsinki, and was approved by the local Ethics Committee (registration HU BI10-002), and all participants provided written informed consent.

Genotyping

For genotype analysis, genomic DNA was obtained from peripheral blood samples either using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol or using TSNT lysis buffer (1% Triton, 1% sodium dodecyl sulfate, 100 mM NaCl, 10 mM Tris-HCl [pH 8.0], and 1 mM EDTA) followed by phenol-chloroform extraction and ethanol precipitation. The extracted DNA was stored at -20°C until use. Analysis of *MDR1* C3435T polymorphism was performed using the PHARMAchip® DNA microarray following the manufacturer's protocols (Progenika Biopharma SA, Derio, Spain).

Statistical analysis

The difference in genotype or allele frequencies between breast cancer patients and control subjects was analyzed by a Crosstab and Pearson's chi-square test. The data were input to the Statistical Package for Social Sciences software (SPSS, Windows version release 22.0; SPSS Inc.; Chicago, IL) for handling and further statistical analyses. Hardy-Weinberg equilibrium was examined by the Chi-square test using the public software developed by Tim M. Strom and Thomas F. Wienker (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the polymorphism and cancer risk (Epi Info program version 7.1.3, CDC, Atlanta, GA, USA). Statistical significance was set at $P<0.05$ for all tests, and all test were two-sided.

Results

The distribution of *MDR1* C3435T genotype in patients ($P = 0.048$) but not for controls ($P = 0.350$) showed significant deviation from a Hardy-Weinberg equilibrium.

The CC genotype was found in 32.8%, CT genotype was found in 54.2%, and TT genotype was found in only 13.0% in the breast cancer patients. In the control group, frequencies of genotypes were 21.2% for CC, 54.2% for CT and 24.6% for TT. This difference was found to be statistically significant ($P = 0.007$). Furthermore, in the stratified analysis, there were significantly increased risks of breast cancer associated with CT and CC genotypes (OR = 1.88, 95% CI: 1.04-3.39, $P = 0.033$ for CT vs. TT; OR = 2.91, 95% CI: 1.48-5.74, $P = 0.001$ for CC vs. TT).

In the patient group, the C allele frequency was 60.0% and the T allele frequency was 40.0%, and in the control group the frequencies were 48.0% for C allele and 52.0% for T allele. There

was significantly increased risk of breast cancer associated with the C allele (OR = 1.59, 95% CI: 1.16-2.18, P = 0.003). Results are summarized in **Table 1**.

Discussion

Several studies have investigated the relationship between the C3435T polymorphism of the *MDR1* gene and the risk of breast cancer in different populations. The purpose of this study was to determine whether an association exists between this polymorphism and the risk of developing breast cancer in subjects from northeastern Mexico.

Some studies have reported a link between the C3435T polymorphism and the risk of developing breast cancer [8, 9, 11, 14, 17, 18, 21-25, 27], while others have failed to observe an association [10, 12, 13, 15, 16, 19, 20, 26]. Our results indicate that the frequencies of the CC and CT genotypes and of the C allele were significantly higher in breast cancer patients compared to controls (**Table 1**).

P-gp, encoded by *MDR1*, can prevent intracellular accumulation of potentially toxic substances and metabolites [31]. Its dysfunction would reduce the protection for cells and would contribute to development of breast cancer [9, 23]. Functional analyses have shown that the C3435T polymorphism significantly decreases both *MDR1* expression and P-gp activity [32, 33]. Most of the studies that have found a relationship between the C3435T polymorphism and breast cancer have also reported the association of TT genotype and T allele with high risk of developing the disease [9, 11, 14, 17, 21-25, 27].

However, other studies did not establish an association between the C3435T polymorphism and *MDR1* expression or P-gp activity [34, 35]. Furthermore, results obtained by Zubor et al. [8] and Abuhaliema et al. [18] revealed that subjects carrying CC genotype of the C3435T polymorphism had increased risk of breast cancer. Similarly, Ghafouri et al. [19] reported that the frequencies of CC genotype and C allele were higher in patients than in controls, although the differences were not statistically significant. It has been hypothesized that in patients with the CC genotype there might be linkage disequilibrium with other polymorphisms in the *MDR1* gene as well as errors in the post-translational modification in the protein structure of P-gp, which might make it defective [18, 36].

The discrepancies among studies may be due to several factors, including differential exposure to specific environmental agents, variation in methodologies employed, and ethnic differences among analyzed populations. Lu et al. [20], Wang et al. [21], and Sheng et al. [22] found association between the C3435T polymorphism and the risk of breast cancer in Caucasians but not in Asians. More recently, Tazzite et al. [24] found that patients with TT genotype had a significantly increased risk of breast cancer in Asians, Caucasians, and North African but not among mixed populations. Thus, ethnicity might have a great effect on the relationship between the C3435T polymorphism and breast cancer risk.

In Mexico, two related studies have been carried out, in which only subjects from the central-western area of the country were analyzed. Macías-Gómez et al. [26] showed that there was no significant difference between breast cancer patients and control groups for the C3435T polymorphism. Gutierrez-Rubio et al. [27] did not find differences in the presence of this polymorphism between total breast cancer cases and the reference group. However, premenopausal T allele carriers showed a 2-fold increased risk of breast cancer with respect to the reference and post-menopausal groups. The differences between these studies and our results are most probably related to ethnicity.

The Mexican population has a high degree of genetic variability. Mestizos constitute the main population in Mexico resulting from admixture between Spaniards, Amerindians, and Africans, principally [37]. Analyses with autosomal short tandem repeats (STRs) have demonstrated significant differences in ancestral components of Mestizo populations throughout the Mexican territory, displaying an increasing North-to-South gradient of Amerindian ancestry, and vice versa regarding the European component [38]. Moreno-Estrada et al. examined local patterns of variation from nearly 1 million genome-wide autosomal SNPs for individuals from several populations, covering most geographic regions of Mexico. They demonstrated a high degree of fine-scale genomic structure across

the country, shaped by pre-Columbian population dynamics and affecting the present-day genomes of Mexican mestizos, which is of both anthropological and biomedical relevance. The study unveiled genetic differences among Mexicans as extensive as the variations between some Europeans and Asians [39]. The genetic variability among Mexicans from different regions of the country has been corroborated with analyses of other genetic systems, such as mitochondrial DNA (mtDNA) [40], and Y-chromosome markers, including Y-STRs [41] and Y-SNPs [42].

Our study examined subjects from northeastern Mexico, whereas in the previous studies [26, 27] subjects from the country's central-western zone were analyzed. Thus, ethnic diversity may have contributed to the discrepancies observed between these studies. In fact, we previously investigated the relationship between several genetic polymorphisms and breast cancer in northeastern Mexico and found significant differences with populations from central [28] and central-western [29] areas of the country.

In conclusion, we analyzed the association between the *MDR1* C3435T polymorphism and the risk of developing breast cancer in subjects from northeastern Mexico. A significant increase in the risk of developing breast cancer was associated with the presence of the CC and CT genotypes and of the C allele. Identification of inter-individual variability in *MDR1* C3435T polymorphism may be useful for individualizing breast cancer genetic screening and therapeutic intervention. Further studies estimating the effect of gene-gene and gene-environment interactions may provide a better understanding of the role of *MDR1* C3435T polymorphism in breast cancer predisposition.

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Disclosure of conflict of interest

None.

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References

[1] DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO and Jemal A. International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev 2015; 24: 1495-1506.

[2] Kelada SN, Eaton DL, Wang SS, Rothman NR and Khoury MJ. The role of genetic polymorphisms in environmental health. Environ Health Perspect 2003; 111: 1055-1064.

[3] Mizutani T, Masuda M, Nakai E, Furumiya K, Togawa H, Nakamura Y, Kawai Y, Nakahira K, Shinkai S and Takahashi K. Genuine functions of P-glycoprotein (ABCB1). Curr Drug Metab 2008; 9: 167-174.

[4] Chufan EE, Sim HM and Ambudkar SV. Molecular basis of the polyspecificityof P-glycoprotein (ABCB1): recent biochemical and structural studies. Adv Cancer Res 2015; 125: 71-96.

[5] Breier A, Barancík M, Sulová Z and Uhrík B. P-glycoprotein-implications of metabolism of neoplastic cells and cancer therapy. Curr Cancer Drug Targets 2005; 5: 457-468.

[6] Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV and Gottesman MM. A "silent" polymorphism in the MDR1 gene changes substrate specificity. Science 2007; 315: 525-528.

[7] Hemauer SJ, Nanovskaya TN, Abdel-Rahman SZ, Patrikeeva SL, Hankins GD and Ahmed MS. Modulation of human placental P-glycoprotein expression and activity by MDR1 gene polymorphisms. Biochem Pharmacol 2010; 79: 921-925.

[8] Zubor P, Lasabova Z, Hatok J, Stanclova A and Danko J. A polymorphism C3435T of the MDR-1 gene associated with smoking or high body mass index increases the risk of sporadic breast cancer in women. Oncol Rep 2007; 18: 211-217.

[9] Turgut S, Yaren A, Kursunluoglu R and Turgut G. MDR1 C3435T polymorphism in patients with breast cancer. Arch Med Res 2007; 38: 539-544.

[10] Henríquez-Hernández LA, Murias-Rosales A, Hernández González A, Cabrera De León A, Díaz-Chico BN, Mori De Santiago M and Férnandez-Pérez L. Gene polymorphisms in TYMS, MTHFR, p53 and MDR1 as risk factors for breast cancer: a case-control study. Oncol Rep 2009; 22: 1425-1433.

[11] George J, Dharanipragada K, Krishnamachari S, Chandrasekaran A, Sam SS and Sunder E. A single-nucleotide polymorphism in the MDR1

gene as a predictor of response to neoadjuvant chemotherapy in breast cancer. Clin Breast Cancer 2009; 9: 161-165.
[12] Tatari F, Salek R, Mosaffa F, Khedri A and Behravan J. Association of C3435T single-nucleotide polymorphism of MDR1 gene with breast cancer in an Iranian population. DNA Cell Biol 2009; 28: 259-263.
[13] Taheri M, Mahjoubi F and Omranipour R. Effect of MDR1 polymorphism on multidrug resistance expression in breast cancer patients. Genet Mol Res 2010; 9: 34-40.
[14] Cizmarikova M, Wagnerova M, Schonova L, Habalova V, Kohut A, Linkova A, Sarissky M, Mojzis J, Mirossay L andMirossay A. MDR1 (C3435T) polymorphism: relation to the risk of breast cancer and therapeutic outcome. Pharmacogenomics J 2010; 10: 62-69.
[15] Rybárová S, Vecanová J, Hodorová I, Mihalik J, Čižmáriková M, Mojžiš J, Solár P, Benický M, Adamkov M and Mirossay L. Association between polymorphisms of XRCC1, p53 and MDR1 genes, the expression of their protein products and prognostic significance in human breast cancer. Med Sci Monit 2011; 17: 354-363.
[16] Rubiś B, Hołysz H, Barczak W, Gryczka R, Łaciński M, Jagielski P, Czernikiewicz A, Półrolniczak A, Wojewoda A, Perz K, Białek P, Morze K, Kanduła Z, Lisiak N, Mrozikiewicz PM, Grodecka-Gazdecka S and Rybczyńska M. Study of ABCB1 polymorphism frequency in breast cancer patients from Poland. Pharmacol Rep 2012; 64: 1560-1566.
[17] Wu H, Kang H, Liu Y, Tong W, Liu D, Yang X, Lian M, Yao W, Zhao H, Huang D, Sha X, Wang E and Wei M. Roles of ABCB1 gene polymorphisms and haplotype in susceptibility to breast carcinoma risk and clinical outcomes. J Cancer Res Clin Oncol 2012; 138: 1449-1462.
[18] Abuhaliema AM, Yousef AM, El-Madany NN, Bulatova NR, Awwad NM, Yousef MA and Al Majdalawi KZ. Influence of genotype and haplotype of MDR1 (C3435T, G2677A/T, C1236T) on the incidence of breast cancer-a case-control study in Jordan. Asian Pac J Cancer Prev 2016; 17: 261-266.
[19] Ghafouri H, Ghaderi B, Amini S, Nikkhoo B, Abdi M and Hoseini A. Association of ABCB1 and ABCG2 single nucleotide polymorphisms with clinical findings and response to chemotherapy treatments in Kurdish patients with breast cancer. Tumour Biol 2016; 37: 7901-7906.
[20] Lu PH, Wei MX, Yang J, Liu X, Tao GQ, Shen W and Chen MB. Association between two polymorphisms of ABCB1 and breast cancer risk in the current studies: a meta-analysis. Breast Cancer Res Treat 2011; 125: 537-543.
[21] Wang J, Wang B, Bi J, Li K and Di J. MDR1 gene C3435T polymorphism and cancer risk: a meta-analysis of 34 case-control studies. J Cancer Res Clin Oncol 2012; 138: 979-989.
[22] Sheng X, Zhang L, Tong N, Luo D, Wang M, Xu M and Zhang Z. MDR1 C3435T polymorphism and cancer risk: a meta-analysis based on 39 case-control studies. Mol Biol Rep 2012; 39: 7237-7249.
[23] Wang Z, Wang T and Bian J. Association between MDR1 C3435T polymorphism and risk of breast cancer. Gene 2013; 532: 94-99.
[24] Tazzite A, Kassogue Y, Diakité B, Jouhadi H, Dehbi H, Benider A and Nadifi S. Association between ABCB1 C3435T polymorphism and breast cancer risk: a Moroccan case-control study and meta-analysis. BMC Genet 2016; 17: 126.
[25] Sharif A, Kheirkhah D, Reza Sharif M, Karimian M and Karimian Z. ABCB1-C3435T polymorphism and breast cancer risk: a case-control study and a meta-analysis. J BUON 2016; 21: 1433-1441.
[26] Macías-Gómez NM, Gutiérrez-Angulo M, Leal-Ugarte E, Ramírez-Reyes L, Peregrina-Sandoval J, Meza-Espinoza JP, Ramos Solano F, de la Luz Ayala-Madrigal M and Santoyo Telles F. MDR1 C3435T polymorphism in Mexican patients with breast cancer. Genet Mol Res 2014; 13: 5018-5024.
[27] Gutierrez-Rubio SA, Quintero-Ramos A, Durán-Cárdenas A, Franco-Topete RA, Castro-Cervantes JM, Oceguera-Villanueva A, Jiménez-Pérez LM, Balderas-Peña LM, Morgan-Villela G, Del-Toro-Arreola A and Daneri-Navarro A. 1236 C/T and 3435 C/T polymorphisms of the ABCB1 gene in Mexican breast cancer patients. Genet Mol Res 2015; 14: 1250-1259.
[28] Jaramillo-Rangel G, Ortega-Martínez M, Cerda-Flores RM and Barrera-Saldaña HA. Polymorphisms in GSTM1, GSTT1, GSTP1, and GSTM3 genes and breast cancer risk in northeastern Mexico. Genet Mol Res 2015; 14: 6465-6471.
[29] Jaramillo-Rangel G, Ortega-Martínez M, Cerda-Flores RM and Barrera-Saldaña HA. Polymorphism in the 3'-UTR of the thymidylate synthase gene and breast cancer risk in northeastern Mexico. Int J Clin Exp Med 2017; 10: 12600-12604.
[30] Alcazar-González GA, Calderón-Garcidueñas AL, Garza-Rodríguez ML, Rubio-Hernández G, Escorza-Treviño S, Olano-Martin E, Cerda-Flores RM, Castruita-Avila AL, González-Guerrero JF, le Brun S, Simon-Buela L and Barrera-Saldaña HA. Comparative study of polymorphism frequencies of the CYP2D6, CYP3A5, CYP2C8 and IL-10 genes in Mexican and Spanish women with breast cancer. Pharmacogenomics 2013; 14: 1583-1592.

[31] Schinkel AH. The physiological function of drug-transporting P-glycoproteins. Semin Cancer Biol 1997; 8: 161-170.

[32] Hoffmeyer S, Burk O, von Richter O, Arnold HP, Brockmöller J, Johne A, Cascorbi I, Gerloff T, Roots I, Eichelbaum M and Brinkmann U. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A 2000; 97: 3473-3478.

[33] Haenisch S, Zimmermann U, Dazert E, Wruck CJ, Dazert P, Siegmund W, Kroemer HK, Warzok RW and Cascorbi I. Influence of polymorphisms of ABCB1 and ABCC2 on mRNA and protein expression in normal and cancerous kidney cortex. Pharmacogenomics J 2007; 7: 56-65.

[34] Uwai Y, Masuda S, Goto M, Motohashi H, Saito H, Okuda M, Nakamura E, Ito N, Ogawa O and Inui K. Common single nucleotide polymorphisms of the MDR1 gene have no influence on its mRNA expression level of normal kidney cortex and renal cell carcinoma in Japanese nephrectomized patients. J Hum Genet 2004; 49: 40-45.

[35] Jamroziak K, Balcerczak E, Cebula B, Janus A, Mirowski M and Robak T. No influence of 3435C>T ABCB1 (MDR1) gene polymorphism on risk of adult acute myeloid leukemia and P-glycoprotein expression in blast cells. Ther Drug Monit 2006; 28: 707-711.

[36] Chen G, Quan S, Hu Q, Wang L, Xia X and Wu J. Lack of association between MDR1 C3435T polymorphism and chemotherapy response in advanced breast cancer patients: evidence from current studies. Mol Biol Rep 2012; 39: 5161-5168.

[37] Gorodezky C, Alaez C, Vázquez-García MN, de la Rosa G, Infante E, Balladares S, Toribio R, Pérez-Luque E and Muñoz L. The genetic structure of Mexican Mestizos of different locations: tracking back their origins through MHC genes, blood group systems, and microsatellites. Hum Immunol 2001; 62: 979-991.

[38] Rubi-Castellanos R, Martínez-Cortés G, Muñoz-Valle JF, González-Martín A, Cerda-Flores RM, Anaya-Palafox M and Rangel-Villalobos H. Pre-Hispanic Mesoamerican demography approximates the present-day ancestry of Mestizos throughout the territory of Mexico. Am J Phys Anthropol 2009; 139: 284-294.

[39] Moreno-Estrada A, Gignoux CR, Fernández-López JC, Zakharia F, Sikora M, Contreras AV, Acuña-Alonzo V, Sandoval K, Eng C, Romero-Hidalgo S, Ortiz-Tello P, Robles V, Kenny EE, Nuño-Arana I, Barquera-Lozano R, Macín-Pérez G, Granados-Arriola J, Huntsman S, Galanter JM, Via M, Ford JG, Chapela R, Rodriguez-Cintron W, Rodríguez-Santana JR, Romieu I, Sienra-Monge JJ, del Rio Navarro B, London SJ, Ruiz-Linares A, Garcia-Herrera R, Estrada K, Hidalgo-Miranda A, Jimenez-Sanchez G, Carnevale A, Soberón X, Canizales-Quinteros S, Rangel-Villalobos H, Silva-Zolezzi I, Burchard EG and Bustamante CD. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science 2014; 344: 1280-1285.

[40] Martínez-Cortés G, Salazar-Flores J, Haro-Guerrero J, Rubi-Castellanos R, Velarde-Félix JS, Muñoz-Valle JF, López-Casamichana M, Carrillo-Tapia E, Canseco-Avila LM, Bravi CM, López-Armenta M and Rangel-Villalobos H. Maternal admixture and population structure in Mexican-Mestizos based on mtDNA haplogroups. Am J Phys Anthropol 2013; 151: 526-537.

[41] Salazar-Flores J, Dondiego-Aldape R, Rubi-Castellanos R, Anaya-Palafox M, Nuño-Arana I, Canseco-Avila LM, Flores-Flores G, Morales-Vallejo ME, Barojas-Pérez N, Muñoz-Valle JF, Campos-Gutiérrez R and Rangel-Villalobos H. Population structure and paternal admixture landscape on present-day Mexican-Mestizos revealed by Y-STR haplotypes. Am J Hum Biol 2010; 22: 401-409.

[42] Martínez-Cortés G, Salazar-Flores J, Fernández-Rodríguez LG, Rubi-Castellanos R, Rodríguez-Loya C, Velarde-Félix JS, Muñoz-Valle JF, Parra-Rojas I and Rangel-Villalobos H. Admixture and population structure in Mexican-Mestizos based on paternal lineages. J Hum Genet 2012; 57: 568-574.