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Genetic structure of Mexican Mestizos with type 2 diabetes mellitus based on three STR loci

Ricardo M. Cerda-Flores [a,*], Roxana A. Rivera-Prieto [b], Benito Pereyra-Alférez [b], Ana L. Calderón-Garcidueñas [c], Hugo A. Barrera-Saldaña [d], Hugo L. Gallardo-Blanco [e], Rocío Ortiz-López [f], Yolanda Flores-Peña [a], Velia M. Cárdenas-Villarreal [a], Fernando Rivas [g], Andrés Figueroa [h], Gautam Kshatriya [i]

[a] Universidad Autónoma de Nuevo León, Facultad de Enfermería, Monterrey, Mexico
[b] Universidad Autónoma de Nuevo León, Facultad de Ciencias Biológicas, Monterrey, Mexico
[c] Universidad Veracruzana, Instituto de Medicina Forense, Veracruz, Mexico
[d] Universidad Autónoma de Nuevo León, Facultad de Medicina, Departamento de Bioquímica y Medicina Molecular, Monterrey, Mexico
[e] Universidad Autónoma de Nuevo León, Hospital Universitario, Departamento de Genética, Monterrey, Mexico
[f] Universidad Autónoma de Nuevo León, Centro de Investigación y Desarrollo en Ciencias de la Salud, Monterrey, Mexico
[g] Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Mexico
[h] Department of Computer Science, University of Texas-Pan American, USA
[i] Department of Anthropology, University of Delhi, Delhi, India

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ABSTRACT

Background: The aims of this population genetics study were: 1) to ascertain whether Mexicans with type 2 diabetes mellitus (DM) were genetically homogeneous and 2) to compare the genetic structure of this selected population with the previously reported data of four random populations (Nuevo León, Hispanics, Chihuahua, and Central Region of Mexico).
Methods: A sample of 103 unrelated individuals with DM and whose 4 grandparents were born in five zones of Mexico was interviewed in 32 Medical Units in the Mexican Institute of Social Security (IMSS). The non-coding STRs D16S539, D7S820, and D13S317 were analyzed.
Results: Genotype distribution was in agreement with Hardy–Weinberg expectations for all three markers. Allele frequencies were found to be similar between the selected population and the four random populations. Gene diversity analysis suggested that more than 99.57% of the total gene diversity could be attributed to variation between individuals within the population and 0.43% between the populations.
Conclusions: According to the present and previous studies using molecular and non-molecular nuclear DNA markers not associated with any disease, the Mexican Mestizo population is found to be genetically homogeneous and therefore the genetic causes of DM are less heterogeneous, thereby simplifying genetic epidemiological studies as has been found in a previous study with the same design in Mexican women with breast cancer.
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1. Introduction

In Mexico, there are 112,322,757 inhabitants, 51.22% women and 48.78% men (Censo de Población y Vivienda, 2010).

In previous studies using non-molecular nuclear DNA markers, we showed that populations of Northeastern Mexico (grouped by birthplace of the four grandparents and birth year) are similar in terms of the contribution of Spanish and Native American genes. More than 96% of the total genetic diversity (G_{ST}) could be attributed to individual variation within the populations defined by birthplaces and/or birth year. There was no nonrandom association of alleles among the genetic marker systems despite the Mestizo origin of the study population (Cerda-Flores and Garza-Chapa, 1989; Cerda-Flores et al., 1987, 1991).

Also, Cerda-Flores et al. (2002a, 2002b) compared genetic polymorphisms at the D1S80 and HLA-DQA1 loci in three unrelated and

Abbreviations: CHIH., Chihuahua; CRMx, Central Region of Mexico; DF, Degree of freedom; DM, Type 2 diabetes mellitus; Exp., Expected; Gst, Total genetic diversity; Ht, Total average gene diversity; HWE, Hardy–Weinberg expectations; IMSS, Mexican Institute of Social Security; LRT, Likelihood ratio test; N.L., Nuevo León; NEGST, Nested gene diversity; Obs., Observed; P, Probability value; PC1, Principal component 1; PC2, Principal component 2; PCR, Polymerase chain reaction; STR, Short tandem repeats; TFA, Fast technology for analysis of nucleic acids; X^2, Chi squared test; CI, Coefficient interval.

* Corresponding author at: Universidad Autónoma de Nuevo León, Facultad de Enfermería, Av. Gonzalitos No. 1500 Norte, Colonia Mitras Centro, C.P. 64460, Monterrey, Nuevo León, Mexico. Tel./fax: +52 81 83481847.

E-mail addresses: ricardocerda_mx@yahoo.com.mx (R.M. Cerda-Flores), roxriverapprieto@hotmail.com (R.A. Rivera-Prieto), bpereyra@gmail.com (B. Pereyra-Alférez), acald911@hotmail.com (A.L. Calderón-Garcidueñas), habarrera@gmail.com (H.A. Barrera-Saldaña), hugoleonid2008@gmail.com (H.L. Gallardo-Blanco), rortizlopez@gmail.com (R. Ortiz-López), yflores_mx@yahoo.com.mx (Y. Flores-Peña), velia_margaritac@hotmail.com (V.M. Cárdenas-Villarreal), genesmx@hotmail.com (F. Rivas), andresfila@utpa.edu (A. Figueroa), g26_51@yahoo.co.in (G. Kshatriya).

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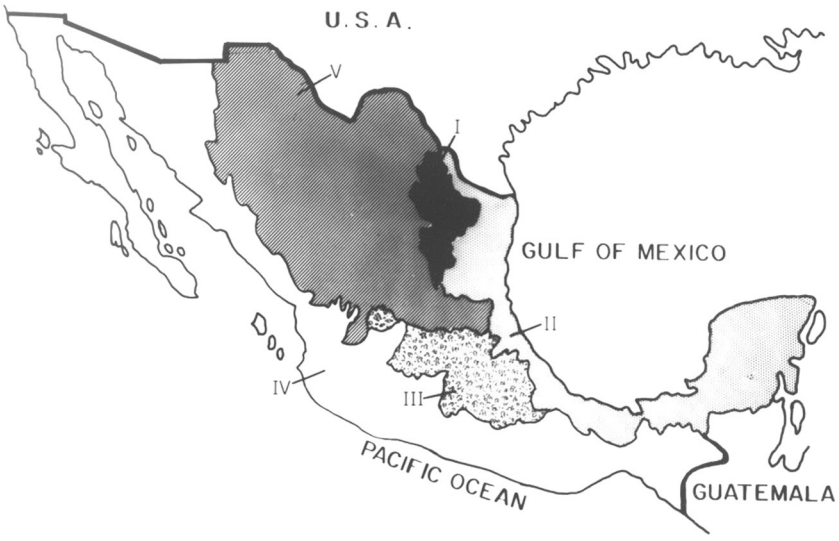

Fig. 1. The location of the five zones of Mexico where the grandparents were born.

healthy Mexican Mestizo populations from three large states (Nuevo León, Jalisco, and the Federal District). Allele frequencies were relatively homogeneous in the three samples. In terms of genetic composition, these Mestizo populations showed evidence of admixture with predominantly Spanish (50–60%) and Native American (37%–49%) contributions; the African contribution (1–3%) was minor.

Cerda-Flores et al. (2002a, 2002b) did not find significant differences when they made a comparison of the genetic admixture among the 143 Mestizos from Northeastern Mexico with the data on previously reported molecular markers, D1S80 and HLA-DQA1 (Spanish 60%, Amerindian 37%, and African 3%) versus 13 short tandem repeat (STR) loci (Spanish 55%, Amerindian 40%, and African 5%).

Type 2 diabetes mellitus (DM) is one of the most common metabolic and endocrinal disorders in developed countries. The prevalence of DM varies widely in populations around the world, with polygenic inheritance and environmental factors contributing to its clinical expression (Bennett and Stern, 1991).

In Mexico, during the 1970s it was the seventh highest, in the 1980s it was the third highest, and in the 1990s it has been considered the highest of all non-communicable diseases (Vazquez-Robles and Escobedo-de la Peña, 1990).

Table 1
Demographic distribution of the zone of birth of the four grandparents of the Mexicans with type 2 diabetes mellitus.

Zone of birth[a]	Maternal		Paternal		Total (%)
	Grandfather	Grandmother	Grandfather	Grandmother	
I	21	22	15	16	74 (19.07)
II	4	5	5	4	18 (4.64)
III	7	7	9	8	31 (7.99)
IV	5	5	5	4	19 (4.90)
V	61	58	63	64	246 (63.40)
Total	98	97	97	96	388
Probability (R × C)	0.9932				

Zone II. Tamaulipas, Veracruz, Yucatán, Campeche, Tabasco, Quintana Roo.
Zone III. Guanajuato, Federal District, Aguascalientes, Puebla, Querétaro, Hidalgo, Tlaxcala, Morelos, Mexico State.
Zone IV. Jalisco, Michoacán, Oaxaca, Nayarit, Guerrero, Colima, Sinaloa, Sonora, Chiapas, Baja California (North and South).
Zone V. San Luís Potosí, Coahuila, Zacatecas, Durango, Chihuahua.
[a] Zone I. Nuevo Leon.

In a previous population genetics study we showed that 115 Mexican women with breast cancer (BC) were genetically homogeneous. The genetic structure of this selected population was similar to four random populations [Nuevo León, Hispanics, Chihuahua, and Central Region of Mexico (CRMx)]. The Spanish and Native American contribution were 40.08 ± 6.17% and 59.92 ± 6.17%, respectively. The design and genetic markers of this previous study was similar to the present study (Calderón-Garcidueñas et al., 2008).

The aims of this population genetics study using the non-coding STRs D16S539, D7S820, and D13S317 that are not associated with DM were: 1) to study the genetic variation in Mexicans with DM; 2) to compute the total contribution of the ancestral populations to this selected population; 3) to evaluate whether there is a residual effect of population admixture on the nonrandom association of alleles; and 4) to compare the observed distribution of the number of heterozygous loci in this population with the data reported in the literature for four random populations [Nuevo León, Hispanics, Chihuahua, and Central Region of Mexico (CRMx)].

2. Materials and methods

Genetic data from this population were collected as part of a larger investigation of the genetic structure of the Mexican Mestizo and Indigenous populations using nuclear DNA, mitochondrial DNA, and Y-chromosome markers.

A sample of 103 unrelated Mexicans with DM (48 men and 65 women), recently diagnosed, was interviewed in 32 Medical Units of the Mexican Institute of Social Security (IMSS) in 2002. Each one of the IMSS Medical Units correspond to each one of the 31 States (capitols) and one Federal District in the entire Mexico.

The study was explained to the patients who were requested to sign an informed consent. The sampled population was interviewed using a structured questionnaire that asked for age, sex, total number of pregnancies, years of education, weight status, civil stage, and place of birth of four grandparents. This study was approved by the Ethical Committee of the IMSS and the Universidad Autonoma de Nuevo Leon.

The data were subgrouped in accordance to the zone of Mexico where the grandparents were born. The country was divided into five zones as is shown in Fig. 1 and Table 1:

I. All in the State of Nuevo León.
II. At least one in the States of Tamaulipas, Veracruz, Yucatan, Campeche or Tabasco.

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Fig. 2. Location of three Mexican Mestizo populations. I. Chihuahua, II. Nuevo León, and Central Region of Mexico (includes the States of Mexico, Morelos, Queretaro, Puebla, and Federal District).

III. At least one in the States of Guanajuato, Federal District, Mexico, Aguascalientes, Puebla, Queretaro, Hidalgo, Tlaxcala or Morelos.
IV. At least one in the States of Jalisco, Michoacán, Oaxaca, Nayarit, Guerrero, Colima, Sinaloa or Sonora, Chiapas, Baja California (North and South).
V. At least one in the States of San Luis Potosi, Coahuila, Zacatecas, Durango, Chihuahua.

All subjects received a medical examination. Both fasting and post-glucose load blood samples were drawn, and diabetes was diagnosed according to the criteria of the World Health Organization Expert Committee (1980).

Whole blood (5 ml) was collected into tubes containing EDTA by venipuncture. After the tubes were gently rotated to ensure that the EDTA and blood were well mixed, plastic pipettes were used to extract blood from the tubes and a large drop (125 μl) was placed onto the center of each of four circles on the commercially prepared FTA® cards (Whatman: WB120206). When blood is spotted onto the FTA paper, cells are lysed, and DNA from the nuclei of the white cells is immobilized within the matrix of the paper. A FTA paper punch was used to cut a 1 mm diameter of paper and the paper washed according to the procedure specified in Budowle et al. (2000) to prepare it for PCR.

Table 2
Genotype frequencies of the D16S539, D7S80, and D13S317 STR markers in 103 Mexicans with diabetes mellitus.

D16S539		D7S80		D13S317	
Genotype	Frequency	Genotype	Frequency	Genotype	Frequency
8/9	1	7/10	1	8/9	5
8/10	1	7/11	1	8/10	2
9/9	2	7/12	1	8/11	1
9/10	7	8/8	1	8/12	3
9/11	6	8/9	2	8/13	1
9/12	9	8/10	8	8/14	1
9/13	2	8/11	12	9/9	2
10/10	2	8/12	1	9/10	5
10/11	6	8/13	1	9/11	9
10/12	7	9/10	3	9/12	17
10/13	6	9/11	7	9/13	8
11/11	8	9/12	1	9/14	3
11/12	26	10/10	5	10/10	1
11/13	9	10/11	18	10/11	2
11/14	1	10/12	12	10/12	10
12/12	10	10/13	2	10/13	1
12/13	8	10/14	2	11/11	4
12/14	1	11/11	12	11/12	15
12/15	1	11/12	15	11/13	2
13/13	2	11/13	3	11/14	3
		11/14	1	12/12	9
		12/12	5	12/13	4
		12/13	1	12/14	5
				13/13	2

2.1. STR amplification

Three CODIS loci (D16S539, D7S820, and D13S317) were typed using the AmpFlSTR™ Profiler Plus™ kit and AmpFlSTR™ Cofiler™ kit (Applied Biosystems, Foster City, CA). The manufacturer's recommended protocols were followed.

2.2. STR typing of profiler plus and cofiler amplified samples

Samples were analyzed using the ABI Prism™ 310 Genetic Analyzer (Applied Biosystems, Forster City, CA). The samples were analyzed using the separation medium Performance Optimized Polymer (POP) 4™ (PE Biosystems, Foster City, CA). The genotypes were recorded with allele designations determined by comparison of the sample fragments with those of the allelic ladder marker (in units of repeat sizes of alleles).

2.3. Statistical analysis

Statistical analyses performed included the following nine steps: First, an $R \times C$ contingency table exact test was used to test for homogeneity of the demographic distribution of the zone of birth of the four grandparents of the 103 Mexicans studied (Roff and Bentzen, 1989). Second, allele frequencies were estimated from the genotypic information previously obtained (Li, 1976). Third, a possible deviation from Hardy–Weinberg expectations (HWE) was tested by three methods: the homozygosity test in which the unbiased estimate of the expected homozygote/heterozygote frequencies (Nei, 1978) were compared with those observed, the likelihood ratio test, LRT (Weir, 1996), and exact test criteria (Guo and Thompson, 1992).

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Table 3
D16S539 allele frequencies in five Mestizo populations and three ancestral populations.

Allele	DM	Nuevo León	Hispanics	Chihuahua	CRMx	Spain	Native American	African
N	103	143	209	161	211	138	874	110
5	.0000	.0000	.0000	.0000	.0024	.0000	.0000	.0045
6	.0000	.0000	.0000	.0000	.0000	.0000	.0000	.0045
8	.0194	.0035	.0168	.0342	.0095	.0237	.0023	.0045
9	.1068	.0979	.0793	.1118	.1090	.1053	.1293	.3000
10	.2087	.1958	.1731	.2019	.1327	.0535	.1751	.0818
11	.3252	.3182	.3149	.2174	.2701	.2961	.1602	.3091
12	.2427	.2692	.2861	.2764	.3318	.3073	.3638	.1273
13	.0922	.0979	.1034	.1398	.1256	.1882	.1545	.1591
14	.0044	.0175	.0240	.0186	.0190	.0243	.0149	.0091
15	.0000	.0000	.0024	.0000	.0000	.0012	.0000	.0000

Fourth, an R × C contingency table exact test was used to test for homogeneity of the five Mestizo populations (DM, Nuevo León, Hispanics, Chihuahua, and CRMx) for D16S539, D7S820, and D13S317 loci separately (Roff and Bentzen, 1989). Fig. 2 shows the location of these populations whose allele frequencies were previously reported: Nuevo León (Cerda-Flores et al., 2002a, 2002b), Chihuahua (Martínez-González et al., 2005), CRMx (Hernández-Gutiérrez et al., 2005), and Hispanics (Budowle et al., 1999, 2001). The Mexican database from the State of Chihuahua was kindly provided by Bruce Budowle of the FBI Laboratory. CRMx includes the States of Mexico, Morelos, Queretaro, Puebla, and Federal District. Fifth, one principal component analysis among eight populations (DM, Chihuahua, Nuevo León, Hispanics, CRMx, Spanish, Native American, and Africans) was done using the SPSS-PC software and the allele frequencies from Tables 2, 3, 4, and 5. Sixth, the percent contribution of ancestral populations to the Mestizo populations was calculated by the method of Elston (1971), each Mestizo population being considered the product of the admixture of three parental populations: Spanish, Native American, and African. As representative of ancestral populations, allele frequency data from the Southwestern region of Spain were obtained from Gamero et al. (2000). Pooled allele frequencies from three Southwestern Native American communities (Apache, Navajo, and Pueblo) represented the Native American ancestral allele frequencies (Budowle et al., 2001). For Africans allele frequencies from Cabinda, Angola were used (Beleza et al., 2004). Seventh, the Mestizo populations were compared using heterogeneity of admixture proportions by the X^2 heterogeneity test (Rao, 1973). Eighth, the extent of genetic variation between populations was assessed using the nested gene diversity computer program (NEGST) developed by Chakraborty et al. (1982). Ninth, computation for nonrandom association of alleles among different genetic loci was conducted according to the methods of Brown et al. (1980) and Chakraborty (1981, 1984) to examine whether any residual effects of admixture remained in the Mexicans studied.

3. Results

The average ages and standard deviation of the patients studied were 60 ± 11 and 54 ± 9 years old for men and women, respectively. Almost 87% were married and the education was predominantly at the level of elementary school (59%). The weight status was evaluated according with the body mass index as 10%, 45.5%, and 44.5% for Normal, Overweight, and Obese, respectively. The distribution of the total number of pregnancies was 0 (3.54%), 1–3 (30.97%), 4–8 (51.33%), and 9–15 (14.16%).

3.1. The distribution of the zone of birth

The distribution of the zone of birth for the four grandparents of each studied Mexican with DM is shown in Table 1. No significant differences were found among the four grandparents when the R × C analysis was applied ($p = 0.993$).

3.2. Allele frequency

The allele frequency estimates for the D16S539, D7S820, and D13S317 loci were used to determine whether the genotype frequencies (Table 2) in this population depart from Hardy–Weinberg proportions. The allele frequencies are in reasonable agreement with their Hardy–Weinberg expectations ($P > 0.05$). Tables 3, 4 and 5 show the allele frequencies of this and four Mestizo populations and the three ancestral populations.

3.3. Gene diversity analysis

The majority (99.57%) of the total average gene diversity ($H_T = 79.6\%$) could be attributed to individual variation within populations

Table 4
D7S820 allele frequencies in five Mestizo populations and three ancestral populations.

Allele	DM	Nuevo León	Hispanics	Chihuahua	CRMx	Spain	Native American	African
N	103	143	209	161	211	138	874	110
6	.0000	.0000	.0024	.0000	.0000	.0000	.0000	.0000
7	.0146	.0140	.0215	.0186	.0095	.0254	.0046	.0136
8	.1019	.0839	.0981	.1460	.1303	.1123	.0950	.1955
9	.0874	.0909	.0478	.0683	.0947	.1449	.0286	.1273
10	.2427	.2902	.3062	.3012	.2204	.2572	.1773	.3227
11	.3058	.2797	.2895	.2702	.3222	.2246	.4073	.2136
12	.2039	.1993	.1914	.1646	.1754	.1739	.2643	.0909
13	.0243	.0385	.0383	.0248	.0450	.0580	.0217	.0318
14	.0194	.0035	.0048	.0062	.0024	.0036	.0011	.0045
15	.0000	.0000	.0000	.0000	.0000	.0000	.0000	.0000

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Table 5
D13S317 allele frequencies in five Mestizo populations and three ancestral populations.

Allele	DM	Nuevo León	Hispanics	Chihuahua	CRMx	Spain	Native American	African
N	103	143	209	161	211	138	874	110
7	.0000	.0000	.0000	.0000	.0000	.0000	.0000	.0045
8	.0825	.0909	.0665	.0683	.0758	.1340	.0240	.0136
9	.2427	.2308	.2192	.2298	.1896	.0725	.2529	.0091
10	.1068	.0699	.1010	.0963	.1090	.0725	.1030	.0227
11	.2379	.1958	.2020	.2640	.2322	.2754	.2334	.3455
12	.1456	.2517	.2167	.1801	.2654	.2971	.2311	.3909
13	.1262	.1224	.1379	.0963	.0900	.1159	.1384	.1546
14	.0534	.0385	.0567	.0652	.0261	.0326	.0160	.0546
15	.0049	.0000	.0000	.0000	.0118	.0000	.0011	.0045

(Table 6). Only a small contribution to the total variability (0.43%) comes from variation between five Mestizo populations.

3.4. Principal component analysis

For the eight populations (five Mestizos and three ancestral), the first two principal components account for 95.29% of the total variation in the sample. This analysis shows that the five Mestizo populations are very close to each other and intermediate to the Spanish and Native American populations. The African contribution was the least and the five Mestizo populations are far from this ancestral population.

3.5. Genetic admixture analysis

In the present investigation we considered the five Mestizo populations as the product of admixture of three parental populations having Spanish, Native American, and African ancestry. The allele frequencies of the Mestizo and ancestral populations for D16S539, D7S820, and D13S317 are presented in Tables 3, 4, and 5, respectively. Since the African contribution was the least as was shown in Fig. 3 by the principal component analysis, this population was discarded and instead of the trihybrid model, the dihybrid model of Elston was applied. Table 7 presents the estimated values of admixture based on three genetic loci. The Spanish (40–47%) and Native American (53–60%) contribution were similar in all the Mestizo populations ($X^2 = 0.73$; $P = 0.95$).

3.6. Nonrandom association among genetic loci

It is well known that the admixture of populations with different allele frequencies can produce nonrandom association of alleles at two or more unlinked loci (Chakraborty and Weiss, 1988; Nei and Li, 1973). From the available genotype data on each patient with DM, we defined the multilocus genotype for each patient for the three loci. The number of loci with respect to which the individual was heterozygous was determined. This generated an observed distribution of the number of heterozygous loci across 103 Mexicans with DM. Chakraborty (1981) provided a numerical algorithm to compute the expected distribution for such observations, assuming random association of alleles at the different loci. Table 8 shows the results for four Mestizo populations.

Table 6
Gene diversity analysis of allele frequency data from five[a] Mestizo populations.

STR	Within populations	Gst	Ht
		Between populations	Total gene diversity
D16S539	99.50	0.50	0.781
D7S820	99.66	0.34	0.785
D13S317	99.54	0.46	0.824
Mean	99.57	0.43	0.796
SE	±0.05	±0.05	±0.013

[a] DM, Nuevo León, Chihuahua, Hispanics, and CRMx.

For each population, the observed distribution agrees with the expected values ($p > 0.05$).

For the DM population, the mean number of heterozygous loci is 2.40 and the variance is 0.46. Their expected values (under the random association model) are 2.37 and 0.50, respectively. The 95% confidence limit of the variance is 0.36–0.64. Clearly, these values provide no evidence of nonrandom association of the alleles among the three polymorphic loci in the DM population whose four grandparents were born in five zones of Mexico. When the DM population and the random population (Nuevo León, Chihuahua, and Hispanics) distributions were compared with an $R \times C$, no statistical significance was found ($p = 0.76$).

4. Discussion

The results obtained in this selected population with DM are similar to the four random populations.

The dihybrid model showed an intermediate Native American and Spanish contribution. These results are consistent with previously published data on genetic admixture in Mexican random populations (Cerda-Flores et al., 2002a, 2002b).

The expected and observed distributions of the number of heterozygous loci indicate that there is no residual effect of such admixture on the nonrandomness of allelic associations at the polymorphic loci (Table 8). These results suggest that the admixture occurred sufficiently long ago that at present the Mexican Mestizos with DM are a genetically homogeneous population, at least with respect to the three loci measured. Therefore, there is no statistical significance found when comparing the homogeneous distributions of the DM population and the four random populations.

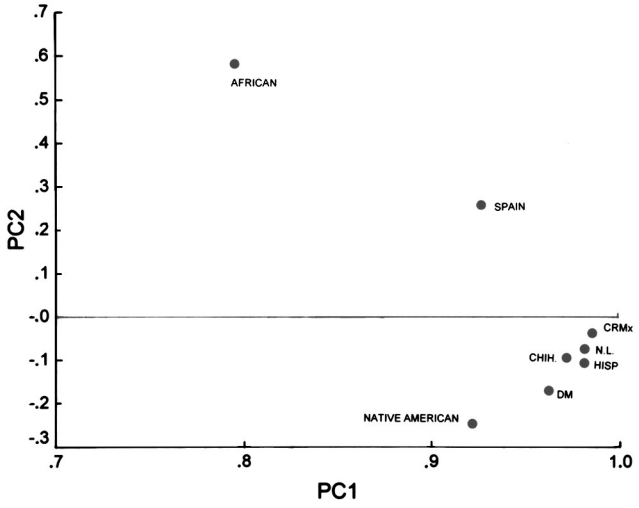

Fig. 3. Position of five Mestizo (DM, Nuevo León, Hispanics, Chihuahua, and CRMx) and three ancestral (Native American, Spain, and African) populations by the first two principal components (PC1 and PC2) of allele frequencies at the D16S539, D7S820, and D13S317 loci.

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Table 7
Percentage contribution from Spanish and Native American gene pools to the five Mestizo populations.

Mestizo population	Spanish	Native American
DM	40.89 ± 5.89	59.11 ± 5.89
Nuevo León	46.26 ± 5.23	53.74 ± 5.23
Chihuahua	43.51 ± 4.92	56.49 ± 4.92
CRMx	46.53 ± 4.48	53.47 ± 4.48
Hispanics	44.61 ± 4.54	55.39 ± 4.54

$X^2 = 0.731$; df = 4, P = 0.9475.

All these results showed a similar ancestral contribution independent of the markers used for evolutionary purposes and all these studies suggest genetic homogeneity (no genetic variation) of the Mexican Mestizo populations, and point towards the utility of this population for genetic and epidemiological studies.

Thus, it appears that Mexican populations with a multifactorial disease and with high prevalence (i.e. type II diabetes mellitus and breast cancer) are genetically homogeneous and could therefore facilitate easy sampling of both affected and control individuals without detailed information of their residential history or inter-state migration history, leading to the possibility for easier collection of large case–control series.

In conclusion, according with this and previous studies using molecular and non-molecular nuclear DNA markers, the Mexican Mestizo population is genetically homogeneous and therefore could be useful for studying genetic causes of diseases, thereby playing an important role in genetic epidemiological studies.

Conflict of interest statement

All the authors guarantee that there are no conflicts of interest.

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Table 8
Observed and expected distribution of the number of heterozygous loci in four Mestizo populations.

Number of heterozygous loci	DM		Nuevo León		Chihuahua		Hispanics	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
0	1	0.97	1	1.29	4	1.23	1	1.77
1	8	10.88	15	14.79	16	15.12	27	20.69
2	43	40.67	53	56.21	60	61.80	74	79.34
3	51	50.49	74	70.71	82	83.86	100	100.20
Total	103		143		162		202	
Mean	2.40	2.37	2.40	2.37	2.36	2.41	2.35	2.38
Variance	0.46	0.50	0.49	0.49	0.57	0.47	0.53	0.49
95% CI for variance	(0.36, 0.64)		(0.38, 0.61)		(0.37, 0.58)		(0.40, 0.59)	
X^2 (df = 3)	0.90		0.40		6.38		2.62	
Probability	0.83		0.94		0.10		0.45	

P = 0.763 (R × C analysis among four Mestizo populations).

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