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# Genetic Differentiation in a Sample from Northern Mexico City Detected by HLA System Analysis: Impact in the Study of Population Immunogenetics

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**ABSTRACT**

The major histocompatibility complex is directly involved in the immune response, and thus the genes coding for its proteins are useful markers for the study of genetic diversity, susceptibility to disease (autoimmunity and infections), transplant medicine, and pharmacogenetics, among others. The polymorphism of the system also allows researchers to use it as a proxy for population genetics analysis, such as genetic admixture and genetic structure. In order to determine the immunogenetic characteristics of a sample from the northern part of Mexico City and to use them to analyze the genetic differentiation from other admixed populations, including those from previous studies of Mexico City population, we analyzed molecular typing results of donors and patients from the Histocompatibility Laboratory of the Central Blood Bank of the Centro Médico Nacional La Raza selected according to their geographic origin. HLA-A, -B, -DRB1, and -DQB1 alleles were typed by polymerase chain reaction with sequence-specific primers. Allelic and haplotype frequencies, as well as population genetics parameters, were obtained by maximum likelihood methods. The most frequent haplotypes found were HLA-A*02/-B*39/-DRB1*04/-DQB1*03:02P, HLA-A*02/-B*35/-DRB1*04/-DQB1*03:02P, HLA-A*68/-B*39/-DRB1*04/-DQB1*03:02P, and HLA-A*02/-B*35/-DRB1*08/-DQB1*04. Importantly, the second most frequent haplotype found in our sample (HLA-A*02/-B*35/-DRB1*04/-DQB1*03:02P) has not been previously reported in any mixed-ancestry populations from Mexico but is commonly encountered in Native American human groups, which can reflect the impact of migration dynamics in the genetic conformation of the northern part of Mexico City, and the limitations of previous studies with regard to the genetic diversity of the analyzed groups. Differences found in haplotype frequencies demonstrated that large urban conglomerates cannot be analyzed as one homogeneous entity but, rather, should be understood as a set of structures in which social, political, and economical factors influence their genesis and dynamics.

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Large urban conglomerates cannot be analyzed as a homogeneous entity from a genetic perspective but, rather, should be understood as a group of biological structures in which social, political, and economic aspects affect their dynamics. These dynamics could modify the distribution of genetic diversity at an intra- and interpopulation level, especially in highly polymorphic systems.

The role genetic variation plays in the human leukocyte antigen (HLA) system is of general interest to the biomedical field, particularly in the study of infectious and autoimmune diseases, pharmacogenetics, and organ donation. This genetic diversity derives from the adaptation of ancestral human groups to different environments around the globe. For decades, extensive studies have been performed on the existence of blocks of two or more HLA loci (Ceppellini et al. 1967; Yunis et al. 2005) and their frequencies varying among different ethnic groups, especially among large continental regions (González-Galarza et al. 2015).

Several studies with genetic markers such as short tandem repeats (STRs), HLA typings (low, intermediate, and high resolution), blood groups, and albumin variants, among others, have previously described Mexico City as having relatively uniform genetics, with Native American (50–60%), European (25–40%), African (4–12%), and Asian (1%) ancestral portions (Lisker et al. 1990; Barquera et al. 2008; Juárez-Cedillo et al. 2008; Zúñiga et al. 2013; Ruíz-Linares et al. 2014). Little is known about the distribution of HLA blocks in the mixed-ancestry populations. Currently, no studies have reported phenomena related to genetic structure in urban settlements using the HLA system as a genetic estimator. These studies would be useful for better organizing suitable stem cell donor banks and umbilical cord blood banks and allocation of deceased donor solid organs available for transplantation.

Demographic factors, such as multiple origins and social stratification of populations, have been demonstrated to play a major role in the distribution of ancestral components within human groups, particularly in urban settlements (Martínez-Marignac et al. 2007; González-Sobrino et al. 2016) that usually are regarded as homogeneous. In the context of internal migration within Mexico, immigration into the metropolitan area of Mexico City (MAMC) is one of the most important processes that have occurred in the country's history (Negrete-Salas 1990). Between 1950 and 1980 the population in the MAMC increased by approximately 4.5 million. The type of industrialization together with economic development and rural migration contributed to the accelerated urban growth during this time (Aguilar and Mateos 2011). A large proportion of immigrants have opted to settle in the northeastern and eastern part of the megalopolis. This tendency has become visible in the municipalities bordering Mexico City's northern city boundaries: between 1950 and 1980 the population living in those municipalities grew from approximately 233,000 to over 5 million people (Cervantes-Sánchez 1988). An increase of 11 million persons in the MAMC population occurred over the past 30 years, with around 9.2 million inhabitants settling in northern Mexico City (Figure 1), bringing to the MAMC a predominantly Native American component, given the demographic characteristics of MAMC immigrants (Negrete-Salas 1990). Furthermore, this region of Mexico City is inhabited mainly by individuals that can be grouped in one of the following clusters (Aguilar and Mateos 2011) according to a selection of weighted median values of socioeconomic stratification classifier variables (Ruvalcaba and Schteingart 2000): (1) a peripheral marginal urban-rural cluster (high incidence of inner migration, low salaries, high occupation rates, and extreme peripheral occupation in close contact with rural zones); (2) a cluster of employees living in large building complexes (an important component of inner migration, high population densities); and (3) a cluster denominated by the peripheral working class (certain presence of inner migration, special distribution in urban concentrations in the peripheral regions of the MAMC). These socially and demographically defined clusters have two common characteristics: they have a lower economic income (for clusters 1 and 3, less than the minimal wage of $80.04 pesos [~$3.90 USD] per hour, as of 1 January 2017 [Comisión Nacional de los Salarios Mínimos]; for cluster 2, less than five times the minimal wage) and a high incidence of migrants from other states into this region (Aguilar and Mateos 2011).

Because this region has recently undergone intense immigration, it is of interest to assess the impact of immigration in the genetic pool of the region and how it affects evaluating the probability of

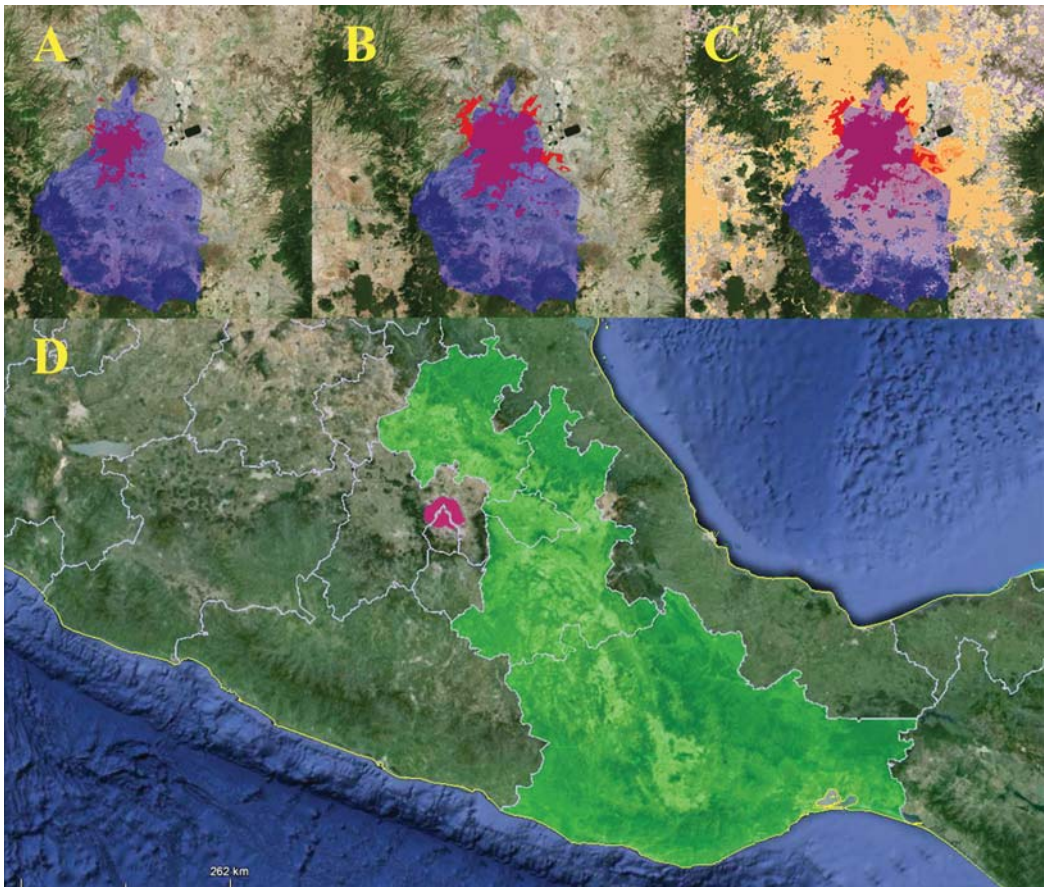


**FIGURE 1.** (A–C) Mexico City's urban extent (red) in 1950 (A) and 1970 (B), and the urban extent in 2014 (orange; red corresponds to 1970 urban extent). The Federal District (currently named "Mexico City" as a state) is depicted in blue for reference. (D) Main interstate migratory flux (Partida 2001) to northern Mexico City, 1995–2000. States from which population come into Mexico City are shown in light green; pink represents the region of northern metropolitan area of Mexico City where they principally settle (Aguilar and Mateos 2011). Maps are modified from Google Earth (version 5.2.1.1588) and Environmental Systems Research Institute, Inc. (2014).

finding a suitable donor in the general population for transplantation procedures of both solid organs and hematopoietic precursors. The aim of the present work is to determine the immunogenetic characteristics of a sample set from the northern region of Mexico City. We then use these characteristics to analyze the differentiation of this part of the city, in comparison to previous HLA-based population genetics studies of mixed-ancestry populations. Our hypothesis is that if the HLA system is analyzed with a set of genetic differentiation tests, then the northern part of Mexico City will be distinguished from other mixed-ancestry populations, including previous samples from Mexico City. This would be explained by differences in the proportions of biological ancestral components (Native American, African, and European) that are heterogeneously distributed within the MAMC and promoted by differential immigration into specific regions of the megalopolis.

## Materials and Methods

### Samples

HLA typings of 344 patients or donors from the Histocompatibility Laboratory, Central Blood Bank, Centro Médico Nacional La Raza (Instituto Mexicano del Seguro Social) gave informed consent to participate in the study and were selected accordingly to their place of origin. We selected only non-genetically related individuals living in the mayoralties of the northern part of Mexico City (Azcapotzalco, Gustavo A. Madero, and Iztacalco)

and the municipalities of the state of Mexico belonging to the MAMC (Naucalpan, Tlalnepantla, Ecatepec, Coacalco, Cuautitlán, Atizapán, and Tultitlán) (Cervantes-Sánchez 1988).

### HLA Typing

HLA typing was performed on DNA extracted through a salting out procedure from blood samples obtained by venous blood collection. The alleles of the *HLA-A*, *-B*, *-DRBI*, and *-DQBI* genes were genotyped by polymerase chain reaction with sequence-specific primers (PCR-SSP) using commercially available validated techniques (AB/DR/DQ SSP Unitray, Life Technologies, Carlsbad, CA, USA; SSP Combi trays, Olerup SSP AB, Stockholm, Sweden) accordingly to the manufacturer's instructions and under American Society for Histocompatibility and Immunogenetics standards. The resolution of HLA typings was kept as informative as possible, and all alleles were classified accordingly to the WHO Nomenclature Committee for Factors of the HLA System (Holdsworth et al. 2009). To comply with HLA nomenclature, ambiguous alleles or alleles that were not able to be called merely based on PCR-SSP typing methods were grouped using G and P codes (Marsh et al. 2010). HLA alleles having identical nucleotide sequences across the exons encoding the peptide-binding domains (exons 2 and 3 for HLA class I alleles and exon 2 for HLA class II alleles) were designated by "G" after the lowest numbered allele; HLA alleles having nucleotide sequences that encode the same protein sequence were designated by "P."

### Statistical Analysis

Allele frequencies and haplotype frequencies (HF) were obtained by direct counting. Haplotypes were analyzed by maximum likelihood (ML) methods using Arlequin (version 3.0; Excoffier et al. 2007). This software was also used to calculate the observed and expected heterozygosity, as well as the Hardy-Weinberg equilibrium (HWE), using $1 \times 10^6$ dememorization steps. Values of $p < 0.05$ between observed and expected heterozygosity were considered statistically significant, indicating a deviation from HWE. Delta and standardized delta ($\Delta'$) values used to measure linkage disequilibrium (LD) were also calculated with Arlequin software. We used previously described methods to estimate $\Delta'$ as a measurement of LD (Cao et al. 2001). Most-probable-ancestry (MPA) haplotypes were assigned based on the frequencies of prior reports (Cao et al. 2001; Yunis et al. 2003, 2005).

Because LD values may result from random associations between two infrequent alleles, our data were validated using the statistical parameter $t$ to adjust values by sample size and number of times each allele appears in the sample (Haseman and Elston 1972; Zúñiga et al. 2013). Only values of $t \geq 2$ were taken as significant.

Linear combinations obtained from dimension reduction of a matrix of 79 populations (including those analyzed in the present work; for the entire list of references, see Supplementary Table 1) and the frequencies of 48 *HLA-B* and *HLA-DRBI* alleles (González-Galarza et al. 2015) were used to graphically differentiate clusters by principal components analysis (PCA) using SPSS Statistics (version 19; IBM Corporation, Armonk, NY, USA) (Zúñiga et al. 2013).

Ancestral contribution proportions were estimated from HF arranged by MPA. To provide a valid comparison against previous reports, we analyzed the ancestral genetic composition of our northern Mexico City sample set with admixture estimates obtained using the ML method implemented in LEADMIX (Wang 2003), with $k = 3$ parental populations (African, American, and European) and frequencies of 47 *HLA-B* alleles as a genetic estimator. The European contribution was estimated from a pooled sample ($N$ = 1,439) comprising data from Andalusia (Spain; data collected by López Nevot et al., reported in González-Galarza et al. 2015), the Spanish minority in the Deutsche Knochenmarkspenderdatei donor registry of Germany (Pingel et al. 2013), Portuguese from northern, central, and southern Portugal (Spínola et al. 2002), and northern Italians from Bergamo (Ferrara et al. 1998). The African component brought into the Americas due to slave trade during the colonial period (16th–18th centuries; reviewed in Barquera and Acuña-Alonzo, 2012) was modeled with a pooled sample ($N$ = 1,236) consisting of Fulani, Mossi, and Rimaibe from Burkina Faso (Modiano et al. 2001), Beti from Cameroon (Torimiro et al. 2006), Cape Verde northwestern and southeastern islands (Spínola et al. 2005), Ga-Adangbe from Ghana (Norman et al. 2013), Chaouya from the Atlantic Coast of Morocco (Canossi et al. 2010), Nigerians

**Table 1. Allelic Frequencies (AF) for *HLA-A*, *-B*, *-DRB1*, and *-DQB1* in a Northern Mexico City Sample Set (*N* = 344)**

| HLA-A | | | HLA-B | | | HLA-DRB1 | | | HLA-DQB1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Allele | AF | *n* | Allele | AF | *n* | Allele | AF | *n* | Allele | AF | *n* |
| A*02 | 0.3430 | 236 | B*35 | 0.2195 | 151 | DRB1*04 | 0.3110 | 214 | DQB1*03:02P | 0.2951 | 203 |
| A*24 | 0.1628 | 112 | B*39 | 0.1628 | 112 | DRB1*08 | 0.1759 | 121 | DQB1*03:01P | 0.2151 | 148 |
| A*68 | 0.1584 | 109 | B*40:02P | 0.0770 | 53 | DRB1*14 | 0.0974 | 67 | DQB1*04 | 0.1802 | 124 |
| A*31 | 0.0654 | 45 | B*15:01P | 0.0683 | 47 | DRB1*16 | 0.0683 | 47 | DQB1*02 | 0.1206 | 83 |
| A*01 | 0.0523 | 36 | B*44 | 0.0669 | 46 | DRB1*07 | 0.0610 | 42 | DQB1*06 | 0.0959 | 66 |
| A*30 | 0.0363 | 25 | B*51 | 0.0509 | 35 | DRB1*13 | 0.0581 | 40 | DQB1*05 | 0.0872 | 60 |
| A*29 | 0.0334 | 23 | B*48 | 0.0422 | 29 | DRB1*03:01P | 0.0567 | 39 | DQB1*03:03P | 0.0058 | 4 |
| A*03 | 0.0305 | 21 | B*07 | 0.0378 | 26 | DRB1*01 | 0.0465 | 32 | | | |
| A*11 | 0.0276 | 19 | B*14:02P | 0.0305 | 21 | DRB1*11 | 0.0451 | 31 | | | |
| A*33 | 0.0247 | 17 | B*18 | 0.0276 | 19 | DRB1*15 | 0.0451 | 31 | | | |
| A*26 | 0.0189 | 13 | B*52 | 0.0262 | 18 | DRB1*01:03 | 0.0131 | 9 | | | |
| A*32 | 0.0102 | 7 | B*08 | 0.0189 | 13 | DRB1*10 | 0.0102 | 7 | | | |
| A*23 | 0.0102 | 7 | B*49 | 0.0174 | 12 | DRB1*12 | 0.0073 | 5 | | | |
| A*25 | 0.0087 | 6 | B*13 | 0.0160 | 11 | DRB1*09 | 0.0029 | 2 | | | |
| A*66 | 0.0073 | 5 | B*38 | 0.0131 | 9 | DRB1*03:02P | 0.0015 | 1 | | | |
| A*74 | 0.0029 | 2 | B*40:05 | 0.0131 | 9 | | | | | | |
| A*36 | 0.0029 | 2 | B*50 | 0.0102 | 7 | | | | | | |
| A*34 | 0.0015 | 1 | B*53 | 0.0102 | 7 | | | | | | |
| A*69 | 0.0015 | 1 | B*27 | 0.0087 | 6 | | | | | | |
| A*XX | 0.0015 | 1 | B*57 | 0.0087 | 6 | | | | | | |
| | | | B*15:10P | 0.0073 | 5 | | | | | | |
| | | | B*45 | 0.0073 | 5 | | | | | | |
| | | | B*55 | 0.0073 | 5 | | | | | | |
| | | | B*14:01P | 0.0058 | 4 | | | | | | |
| | | | B*40:01P | 0.0058 | 4 | | | | | | |
| | | | B*41 | 0.0058 | 4 | | | | | | |
| | | | B*15:03P | 0.0044 | 3 | | | | | | |
| | | | B*42 | 0.0044 | 3 | | | | | | |
| | | | B*15:17P | 0.0029 | 2 | | | | | | |
| | | | B*15:48 | 0.0029 | 2 | | | | | | |
| | | | B*37 | 0.0029 | 2 | | | | | | |
| | | | B*58 | 0.0029 | 2 | | | | | | |
| | | | B*73 | 0.0029 | 2 | | | | | | |
| | | | B*15:02P | 0.0015 | 1 | | | | | | |
| | | | B*15:05P | 0.0015 | 1 | | | | | | |
| | | | B*40:08 | 0.0015 | 1 | | | | | | |
| | | | B*40:XX | 0.0015 | 1 | | | | | | |
| | | | B*47 | 0.0015 | 1 | | | | | | |
| | | | B*56 | 0.0015 | 1 | | | | | | |
| | | | B*82 | 0.0015 | 1 | | | | | | |
| | | | B*XX | 0.0015 | 1 | | | | | | |

from the 1000 Genome Project (Gourraud et al. 2014), and Mandenka from Niokholo region, Senegal (Sánchez-Mazas et al. 2000). For the Native American biological component, Nahuas from central Mexico (Vargas-Alarcón et al. 2007); Mixtec (Hollenbach et al. 2001; Arnaiz-Villena et al. 2014) and Mixe and Zapotec (Hollenbach et al. 2001) from Oaxaca in southeast Mexico; Maya from Guatemala (Gómez-Casado et al. 2003); and Tarahumara from Chihuahua in northern Mexico (García-Ortíz et al. 2006) were pooled (*N* = 732).

To statistically demonstrate that the analyzed sample set differed from those previously reported from Mexico City (Barquera et al. 2008; Zúñiga et al. 2013), the exact test of genetic differentiation based on HF (Rousset and Raymond 1995; Goudet

et al. 1996) as implemented in Arlequin with $3 \times 10^6$ steps in the Markov chain.

## Results

In the present study we examined the distribution of HLA genes and haplotypes in a group of Mexican mixed-ancestry individuals from the northern area of Mexico City. Twenty *HLA-A* alleles, 41 *HLA-B* alleles, 15 *HLA-DRBI* alleles, and 7 *HLA-DQBI* alleles were detected, including one new *HLA-A* and one new *HLA-B* allele, as well as a variant of the HLA-B*40 allele, that could not be resolved by PCR-SSP methods (Table 1).

A total of 247 different *HLA-A*/*-B*/*-DRBI*/*-DQBI* haplotypes were found in the northern Mexico City sample set. The analyses of two-point associations between *HLA-A*/*-B*, *HLA-B*/*-DRBI*, and *HLA-DRBI*/*-DQBI* and their statistical parameters are shown in Tables 2–4. Twelve *HLA-A*/*-B* associations had statistically significant *t* values, but only eight had HF > 1.0% (Table 2). Eleven of 13 *HLA-B*/*-DRBI* blocks with statistically significant *t* values had HF > 1.0% (Table 3). All twelve class II associations with statistically significant *t* values had HF > 1.0% (Table 4).

The most relevant haplotypes found in this sample are listed in Table 5, as well as other populations in which each haplotype has been previously reported. The ancestral haplotypic contribution analysis (Figure 2) showed the following percentages: 46.66% Native American (61 different haplotypes), 34.44% European (158 haplotypes), 7.27% Asian (34 haplotypes), and 6.54% African (39 haplotypes). Additionally, 1.60% of the haplotypic diversity has a proposed mixed origin (more than one ancestral component), and 19 haplotypes (3.49%) to the best of our knowledge have not been previously reported. Ancestral proportions obtained by ML estimated 42.44% European, 3.62% African, and 53.95% Native American components.

HWE analysis showed no significant deviations (data not shown; $p > 0.05$ for each locus). A total of 55.86% of the variance was retained by the PCA (component 1: 21.86%; component 2: 34.00%), and our northern MAMC sample shows a displacement compared to previous reports from Mexico City (Figure 3). The exact test of genetic differentiation based on HF further demonstrated that the three samples from Mexico City analyzed were statistically different from each other ($p < 0.0001$).

**Table 2. Most Frequent *HLA-A*/*-B* Associations in a Northern Mexico City Sample Set (*N* = 344)**

| Allele | Haplotype Frequency | *n* | \|Δ´\| | *p* | *t* |
|---|---|---|---|---|---|
| A*02/B*35 | 0.0727 | 50 | 0.0350 | 0.73 | –0.2 |
| A*02/B*39 | 0.0654 | 45 | 0.0894 | 0.15 | 1.1 |
| A*68/B*39 | 0.0465 | 32 | 0.1562 | **<0.01** | **3.0** |
| A*24/B*35 | 0.0436 | 30 | 0.0620 | 0.18 | 1.1 |
| A*24/B*39 | 0.0378 | 26 | 0.0828 | **0.03** | 1.7 |
| A*68/B*35 | 0.0349 | 24 | 0.0009 | 0.98 | 0.0 |
| A*02/B*40:02P | 0.0291 | 20 | 0.0523 | 0.58 | 0.4 |
| A*31/B*35 | 0.0291 | 20 | 0.2882 | **<0.01** | 2.8 |
| A*02/B*51 | 0.0276 | 19 | 0.3042 | **0.01** | **2.2** |
| A*24/B*40:02P | 0.0276 | 19 | 0.2338 | **<0.01** | **2.8** |
| A*02/B*15:01P | 0.0262 | 18 | 0.0608 | 0.55 | 0.5 |
| A*02/B*44 | 0.0247 | 17 | 0.0404 | 0.69 | 0.3 |
| A*02/B*48 | 0.0218 | 15 | 0.2652 | **0.04** | 1.7 |
| A*29/B*44 | 0.0174 | 12 | 0.4875 | **<0.01** | **3.3** |
| A*24/B*15:01P | 0.0145 | 10 | 0.0597 | 0.34 | 0.8 |
| A*31/B*39 | 0.0131 | 9 | 0.0444 | 0.48 | 0.6 |
| A*03/B*07 | 0.0116 | 8 | 0.3566 | **<0.01** | **2.7** |
| A*33/B*14:02P | 0.0116 | 8 | 0.4539 | **<0.01** | 2.8 |
| A*02/B*18 | 0.0102 | 7 | 0.0387 | 0.81 | 0.2 |
| A*02/B*40:05 | 0.0102 | 7 | 0.6618 | **0.01** | **2.6** |
| A*68/B*40:02P | 0.0102 | 7 | 0.1666 | 0.58 | -0.5 |

Boldface values are statistically significant ($p < 0.05$; $t \geq 2$). |Δ´|, absolute value of standardized linkage disequilibrium; *t*, validation statistic.

## Discussion

Even though we found no significant differences regarding the ML admixture estimations between our sample and previous reports, it is notable that haplotypic diversity is more informative than allele-based admixture estimation. Compared with previous reports in Mexican mixed-ancestry individuals (Barquera et al. 2008; Zúñiga et al. 2013), an increase in the quantity and frequency of Native American and African MPA HLA haplotypes can be found compared to European ones. This tendency can result from migratory patterns within the studied region (Negrete-Salas 1990; Partida 2001; Martínez et al. 2003), with individuals coming mainly from states with large indigenous communities (Hidalgo: 30.12%, Oaxaca: 57.95%, Puebla: 25.17%; Instituto Nacional de Estadística y Geografía 2011; Figure 1). Moreover, previous reports examining Mexico City (Barquera et al. 2008; Zúñiga et al.

2013) were statistically different regarding the HLA system and its haplotypes. In the PCA plot, two HLA genes (*HLA-B* and *HLA-DRB1*) were used to differentiate this northern Mexico City sample from previous reports from this region that were thought as a homogeneous system, as well as from other "Mestizo" or "admixed" populations. Other authors (Barquera et al. 2013) have pinpointed the importance of recent human migration into Mexico City (to the extent of actually modifying HWE); nevertheless, the present study is the first to our knowledge to report that genetic analysis focused on immigration into a particular region of an urban settlement plays an important role in spotting the underlying genetic structure regarding the HLA system.

A high presence of two-point associations and haplotypes of Native American MPA, in addition to the statistical differentiation from other samples of the same city, may be explained at the genetic level by these structures within Mexico City (Tables 2–5). Importantly, the second most frequent haplotype found in our sample (HLA-A*02/-B*35/-DRB1*04/-DQB1*03:02P; Table 5) has not been previously reported in any "Mestizo" samples from Mexico (Barquera et al. 2008; Zúñiga et al. 2013) but is commonly reported in Native American groups such as Mazatecan from Mexico (Arnaiz-Villena et al. 2000), Maya from Guatemala (Gómez-Casado et al. 2003), and Uros from Peru (Arnaiz-Villena et al. 2009). This could reflect the impact of migration dynamics in the genetic conformation of the northern part of Mexico City. Given the presence of African-descent populations in the state of Oaxaca, the increase in the frequencies of African MPA haplotypes in this sample set may be due to recent migration of individuals from this state into the studied region. The noticeable presence of Asian MPA haplotypes may be attributable to Filipino migration into Mexico during the colonial period (Mercene 2007) and to Chinese, Japanese, and Korean migrations after changes in foreign affairs laws and policies during the 19th century and the beginning of the 20th century encouraged settlement and naturalization of foreigners, including integration into economic activities (Acosta and Zizumbo 2011; Romero-Estrada 2000).

Mixed-ancestry haplotypes can arise from the complex population dynamics present in this region for over 500 years. Blocks with Native

**Table 3. Most Frequent *HLA-B/-DRB1* Associations in a Northern Mexico City Sample Set (*N* = 344)**

| Allele | Haplotype Frequency | *n* | \|Δ′\| | *p* | *t* |
|---|---|---|---|---|---|
| B*39/DRB1*04 | 0.0858 | 59 | 0.3131 | **<0.01** | **4.2** |
| B*35/DRB1*08 | 0.0669 | 46 | 0.2059 | **< 0.01** | **3.5** |
| B*35/DRB1*04 | 0.0610 | 42 | 0.1058 | 0.32 | –0.7 |
| B*39/DRB1*14 | 0.0392 | 27 | 0.2869 | **<0.01** | **3.8** |
| B*35/DRB1*16 | 0.0378 | 26 | 0.4276 | **<0.01** | **4.0** |
| B*40:02P/DRB1*04 | 0.0363 | 25 | 0.2332 | **0.01** | **2.1** |
| B*44/DRB1*07 | 0.0276 | 19 | 0.4131 | **<0.01** | **4.2** |
| B*15:01P/DRB1*04 | 0.0247 | 17 | 0.0735 | 0.44 | 0.6 |
| B*15:01P/DRB1*08 | 0.0247 | 17 | 0.2255 | **<0.01** | **2.5** |
| B*39/DRB1*08 | 0.0203 | 14 | 0.2893 | 0.12 | –1.3 |
| B*40:02/DRB1*08 | 0.0203 | 14 | 0.1071 | 0.08 | 1.4 |
| B*07/DRB1*15 | 0.0189 | 13 | 0.4764 | **<0.01** | **3.6** |
| B*14:02P/DRB1*01 | 0.0174 | 12 | 0.5505 | **<0.01** | **3.4** |
| B*35/DRB1*14 | 0.0174 | 12 | 0.1839 | 0.40 | –0.7 |
| B*48/DRB1*04 | 0.0174 | 12 | 0.1491 | 0.22 | 1.0 |
| B*48/DRB1*08 | 0.0174 | 12 | 0.2887 | **<0.01** | **2.3** |
| B*08/DRB1*03:01P | 0.0160 | 11 | 0.8369 | **<0.01** | **3.3** |

Boldface values are statistically significant ($p < 0.05$; $t \geq 2$). |Δ′|, absolute value of standardized linkage disequilibrium; *t*, validation statistic.

**Table 4. Most Frequent *HLA-DRB1/-DQB1* Associations in a Northern Mexico City Sample Set (*N* = 344)**

| *Allele* | Haplotype Frequency | *n* | \|Δ′\| | *p* | *t* |
|---|---|---|---|---|---|
| DRB1*04/DQB1*03:02P | 0.2951 | 203 | 1.0000 | **<0.01** | **24.3** |
| DRB1*08/DQB1*04 | 0.1759 | 121 | 1.0000 | **<0.01** | **14.0** |
| DRB1*14/DQB1*03:01P | 0.0901 | 62 | 0.9049 | **<0.01** | **8.7** |
| DRB1*16/DQB1*03:01P | 0.0625 | 43 | 0.8916 | **<0.01** | **7.0** |
| DRB1*07/DQB1*02 | 0.0581 | 40 | 0.9458 | **<0.01** | **6.7** |
| DRB1*03:01P/DQB1*02 | 0.0552 | 38 | 0.9708 | **<0.01** | **6.6** |
| DRB1*01/DQB1*05 | 0.0465 | 32 | 1.0000 | **<0.01** | **6.0** |
| DRB1*13/DQB1*06 | 0.0451 | 31 | 0.7511 | **<0.01** | **5.7** |
| DRB1*15/DQB1*06 | 0.0436 | 30 | 0.9643 | **<0.01** | **5.7** |
| DRB1*11/DQB1*03:01P | 0.0378 | 26 | 0.7945 | **<0.01** | **5.1** |
| DRB1*01:03/DQB1*05 | 0.0131 | 9 | 1.0000 | **<0.01** | **3.1** |
| DRB1*04/DQB1*03:01P | 0.0102 | 7 | 0.8479 | **<0.01** | –5.5 |
| DRB1*10/DQB1*05 | 0.0102 | 7 | 1.0000 | **<0.01** | **2.7** |
| DRB1*13/DQB1*03:01P | 0.0102 | 7 | 0.1865 | 0.52 | –0.6 |

Boldface values are statistically significant ($p < 0.05$; $t \geq 2$). |Δ′|, absolute value of standardized linkage disequilibrium; *t*, validation statistic.

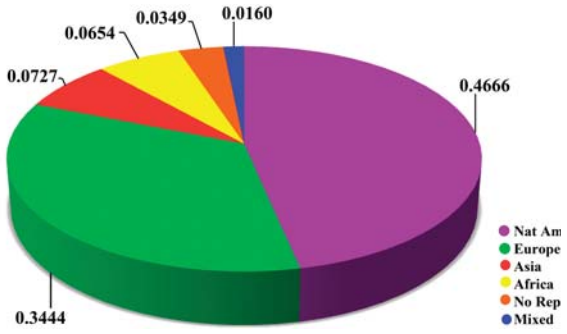


**FIGURE 2.** Haplotypic contributions of most probable ancestry found in a sample from northern Mexico City. Nat Am, Native American; Eur, European; Asi, Asian; Afr, African; No Rep, not previously reported; Mix, mixed ancestry.

**Table 5. Most Frequent *HLA-A/-B/-DRB1/-DQB1* Haplotypes (HF > 0.01) in a Sample Set of Northern Mexico City and Reports in Previous Populations (*N* = 344)**

| Haplotype | | | | HF | *n* | \|Δ´\| | *p* | *t* | Population (Reference), Frequency |
|---|---|---|---|---|---|---|---|---|---|
| A*02 | B*39 | DRB1*04 | DQB1*03:02P | 0.0378 | 26 | 0.1752 | **< 0.01** | **3.0** | Yucpa (Layrisse et al. 2001), 0.257; Sioux (Leffell et al. 2004), 0.051; Mazatecan (Arnaiz-Villena et al. 2000), 0.149; Maya (Gómez-Casado et al. 2003), 0.042; Teenek (Vargas-Alarcón et al. 2003), 0.037; Mexico City (Zúñiga et al. 2013), 0.032; Mexico City (Barquera et al. 2008), 0.029. |
| A*02 | B*35 | DRB1*04 | DQB1*03:02P | 0.0276 | 19 | 0.1752 | **< 0.01** | **3.0** | Teenek (Vargas-Alarcón et al. 2003), 0.155; Maya (Gómez-Casado et al. 2003), 0.106; Uro (Arnaiz-Villena et al. 2009), 0.063; Mixtec (Hollenbach et al. 2001), 0.030; Mazatec (Arnaiz-Villena et al. 2000), 0.025; Nahua (Vargas-Alarcón et al. 2007), 0.020. |
| A*68 | B*39 | DRB1*04 | DQB1*03:02P | 0.0276 | 19 | 0.0109 | 0.85 | 0.1 | Yucpa (Layrisse et al. 2001), 0.337; Maya (Gómez-Casado et al. 2003), 0.064; Teenek (Vargas-Alarcón et al. 2003), 0.052; Mexico City (Barquera et al. 2008), 0.025. Mexico City (Zúñiga et al. 2013), 0.011. |
| A*02 | B*35 | DRB1*08 | DQB1*04 | 0.0262 | 18 | 0.0916 | 0.12 | 1.2 | Mixe (Hollenbach et al. 2001), 0.190; Uro (Arnaiz-Villena et al. 2009), 0.168; Aymara (Arnaiz-Villena et al. 2005), 0.104; Mixtec (Hollenbach et al. 2001), 0.090; Maya (Gómez-Casado et al. 2003), 0.084; Mexico City (Zúñiga et al. 2013), 0.037; Tarahumara (García-Ortiz et al. 2006), 0.034; Yup'ik (Leffell et al. 2002), 0.031. Mexico City (Barquera et al. 2008), 0.012. |
| A*24 | B*35 | DRB1*16 | DQB1*03:01P | 0.0145 | 10 | 0.1923 | **< 0.01** | **3.2** | Yucpa (Layrisse et al. 2001), 0.07; Mexico City (Barquera et al. 2008), 0.017; Puebla (Barquera et al. 2008), 0.015; "Hispanic" (Maiers et al. 2007), 0.014; Mexico City (Zúñiga et al. 2013), 0.009. |
| A*02 | B*40:02P | DRB1*04 | DQB1*03:02P | 0.0145 | 10 | 0.1752 | **< 0.01** | **3.0** | Mexico City (Barquera et al. 2008), 0.012; "Hispanic" (Maiers et al. 2007), 0.001. |
| A*24 | B*39 | DRB1*14 | DQB1*03:01P | 0.0145 | 10 | 0.1923 | **< 0.01** | **3.2** | Mexico City (Zúñiga et al. 2013), 0.026; "Hispanic" (Maiers et al. 2007), 0.006. |
| A*68 | B*35 | DRB1*08 | DQB1*04 | 0.0145 | 10 | 0.1047 | **0.01** | **2.0** | Chuvasian (Arnaiz-Villena et al. 2003), 0.037; Mexico City (Zúñiga et al. 2013), 0.004; "Hispanic" (Maiers et al. 2007), 0.002. |
| A*02 | B*15:01P | DRB1*04 | DQB1*03:02P | 0.0131 | 9 | 0.1752 | **< 0.01** | **3.0** | Murcia (Muro et al. 2001), 0.016; Maya (Gómez-Casado et al. 2003), 0.015. |
| A*68 | B*15:01P | DRB1*08 | DQB1*04 | 0.0131 | 9 | 0.1047 | **0.01** | **2.0** | "Hispanic" (Maiers et al. 2007), < 0.001. |
| A*24 | B*39 | DRB1*04 | DQB1*03:02P | 0.0131 | 9 | 0.0619 | 0.64 | –0.4 | Yucpa (Layrisse et al. 2001), 0.093; Aleut (Moscoso et al. 2008), 0.042; Mazatec (Arnaiz-Villena et al. 2000), 0.033; Sinaloa (Barquera et al. 2008), 0.027; Mexico City (Zúñiga et al. 2013), 0.004. |
| A*24 | B*35 | DRB1*08 | DQB1*04 | 0.0131 | 9 | 0.0851 | **0.04** | 1.6 | Uro (Arnaiz-Villena et al. 2009), 0.068; Yup'ik (Moscoso et al. 2006), 0.06; Mixtec (Hollenbach et al. 2001), 0.050; Maya (Gómez-Casado et al. 2003), 0.042; Aymara (Arnaiz-Villena et al. 2005), 0.031; Lama (Moscoso et al. 2006), 0.024; Mexico City (Zúñiga et al. 2013), 0.004. |
| A*02 | B*39 | DRB1*14 | DQB1*03:01P | 0.0131 | 9 | 0.0939 | 0.35 | –0.7 | Lama (Moscoso et al. 2006), 0.036. Mexico City (Zúñiga et al. 2013), 0.004. |
| A*02 | B*48 | DRB1*04 | DQB1*03:02P | 0.0131 | 9 | 0.1752 | **< 0.01** | **3.0** | Lama (Moscoso et al. 2006), 0.126; "Hispanic" (Maiers et al. 2007), 0.002. |
| A*01 | B*08 | DRB1*03:01P | DQB1*02 | 0.0131 | 9 | 0.2735 | **< 0.01** | **2.8** | Ireland (Dunne et al. 2008), 0.115; England (Alfirevic et al. 2012), 0.095; Macedonia (Arnaiz-Villena et al. 2001), 0.049; Poland (Nowak et al. 2008), 0.040; Basques (Sánchez-Velasco et al. 2003), 0.040; Mexico City (Barquera et al. 2008), 0.012. |
| A*31 | B*35 | DRB1*04 | DQB1*03:02P | 0.0116 | 8 | 0.3380 | **< 0.01** | **2.9** | Sioux (Leffell et al. 2004), 0.041; Maya (Gómez-Casado et al. 2003), 0.026; Mexico City (Barquera et al. 2008), 0.012; "Hispanic" (Maiers et al. 2007), 0. 009; Mexico City (Zúñiga et al. 2013), 0.004. |
| A*24 | B*40:02P | DRB1*04 | DQB1*03:02P | 0.0102 | 7 | 0.0619 | 0.64 | –0.4 | Mixtec (Hollenbach et al. 2001), 0.040; Costa Rica Central Valley (Arrieta-Bolaños et al. 2011), 0.035; Yup'ik (Leffell et al. 2002), 0.022; Puebla (Barquera et al. 2008), 0.020; "Hispanic" (Maiers et al. 2007), 0.001. |
| A*02 | B*51 | DRB1*04 | DQB1*03:02P | 0.0102 | 7 | 0.1752 | **< 0.01** | **3.0** | Sioux (Leffell et al. 2004), 0.014; Turkey (Pingel et al. 2013), 0.005; Mexico City (Zúñiga et al. 2013), 0.004. |
| A*29 | B*44 | DRB1*07 | DQB1*02 | 0.0102 | 7 | 0.2584 | **< 0.01** | **2.1** | Ibiza (Crespí et al. 2002), 0.061; Vizcaya (Crespí et al. 2002), 0.053; Murcia (Crespí et al. 2002), 0.051; Spain (Pingel et al. 2013), 0.028; Mallorca Jews (Crespí et al. 2002), 0.026; Mallorca (Crespí et al. 2002), 0.023; France (Pingel et al. 2013), 0.020; Mexico City (Zúñiga et al. 2013), 0.004. |
| A*24 | B*40:02P | DRB1*08 | DQB1*04 | 0.0102 | 7 | 0.0851 | **0.04** | 1.6 | Tarahumara (García-Ortiz et al. 2006), 0.034; Costa Rica Central Valley (Arrieta-Bolaños et al. 2011), 0.019; "Hispanic" (Maiers et al. 2007), 0.001. |

Boldface values are statistically significant ($p < 0.05$; $t \geq 2$). |Δ´|, absolute value of standardized linkage disequilibrium; *t*, validation statistic.

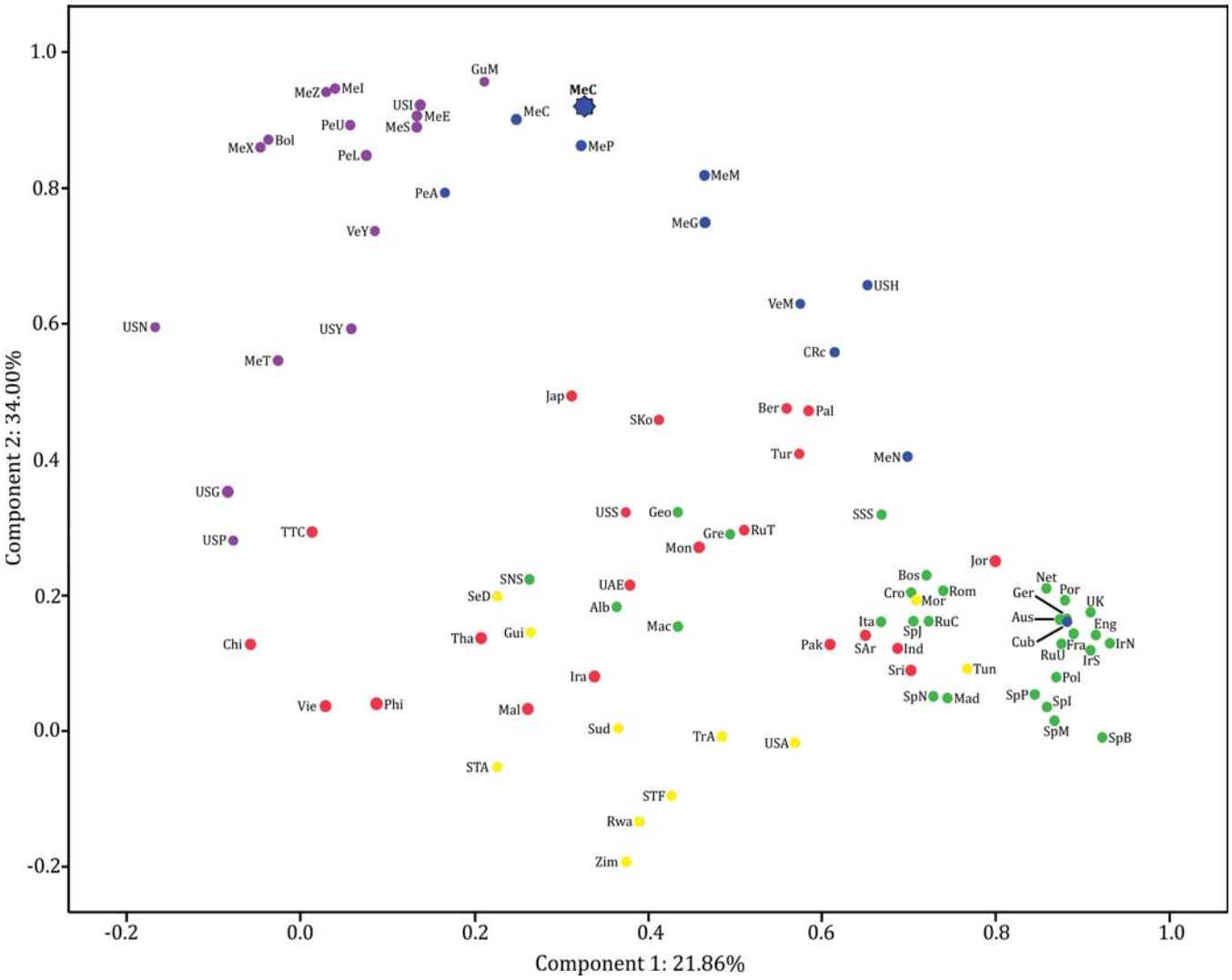


**FIGURE 3.** Principal component analysis plot of 78 populations and 48 *HLA-B* and *HLA-DRB1* alleles. Green dots, European populations; yellow, African populations; red, Asian populations; purple, Native American populations; blue, admixed populations. Our northern Mexico City sample is represented by a blue star. References and *n*-values for all populations are given in Supplementary Table 1. Ale, Germany; Ara, Saudi Arabia; Aus, Austria; Ber, Aleuts from Bering; Bol, Aymara from Bolivia; Bos, Bosnia Herzegovina; Chi, China; CoS, South Korea; CRc, Costa Rica Central Valley; Cro, Croatia; EAU, Arab Emirates; EsJ, Jews from Spain; EsM, Spain (Murcia); EsN, Spain (North); Esp, Spain; EspP, Spain (Pas valley); Fil, Philippines; Fra, France; Gre, Greece; Gua, Maya from Guatemala; Gui, Guinea; Hol, Netherlands; Ibi, Spain (Ibiza); Ira, Iran; Ind, Maratha from India; Ing, NW England; IrN, Northern Ireland; IrS, Ireland; Ita, Italy; Jap, Japan; Jor, Jordan; Mad, Madeira; Mal, Malaysia; Mar, Morocco; MeC, Mexico City (Zúñiga et al. 2013); MeM, Mexico City (Barquera et al. 2008); MeT, Tarahumara from Mexico; MeG, Guadalajara City; MeE, Teenek from Mexico; MeX, Mixe from Mexico; MeI, Mixtec from Mexico; MeZ, Zapotec from Mexico; MeP, Puebla City; MeS, Seris from Mexico; MeN, Sinaloa; Pak, Pakistan; Pal, Palestine; PeA, Peru (Arequipa); PeL, Lama from Peru; PeU, Uro from Peru; Pol, Poland; Por, Portugal; Rua, Rwanda; RuC, Chuvashian from Russia; Rum, Romania; RuU, Russian Urals; STA, Angolar from São Tomé; STF, Forro from São Tomé; Sen, Dakar from Senegal; Sri, Sri Lanka; Sud, Sudan; Tai, Thailand; TTC, Taiwan; Tri, Trinidad and Tobago; Tun, Tunisia; Tur, Turkey; UK, United Kingdom; USY, Yup'ik from Alaska; USG, Gila River Communities; USA; USP, Pima from USA; USN, Navajo from USA; USI, Sioux from USA; Vas, Basques; VeY, Yucpa from Venezuela; VeM, admixed population from Venezuela; Vie, Vietnam; Zim, Zimbabwe.

American MPA are found in LD with European, African, or Asian MPA associations, which suggest that the processes of biologic admixture that have been occurring for the last half millennium can be consistently found at a genomic level within the HLA region. The presence of these "unique" haplotypes in the context of admixed populations indicates a need to update current databases and categories, at least regarding biomedical research studies. It is evident that the concept of "recipient candidate" and "probable donor" should be considered within a novel context in which the

so-called Mestizo populations should be analyzed as a source not only of haplotypes with distinct probable ancestries but also of new haplotypes that may be found only in other populations sharing a similar demographic history. Updates in the data sets of potential hematopoietic cell donors, cadaveric donor programs, and panel reactive antibody analysis are needed to incorporate these mixed-ancestry phenotypes to better provide the biomedical research community with appropriate results.

When all information is considered, it appears that the conclusions drawn from samples from Mexico City as a homogeneous conglomerate (Lisker et al. 1990; Barquera et al. 2008; Juárez-Cedillo et al. 2008; Zúñiga et al. 2013; Ruíz-Linares et al. 2014) cannot be extrapolated to the distinct social, economic, and geographic regions of the megalopolis. This newly identified differentiation should be used to update genetic screening programs dealing with biological variability in patients, such as those assessing the safety and cost-effectiveness of drug administration and pharmacovigilance surveillance systems (Profaizer and Eckels 2012). The demographic history of northern Mexico City can be used to explain the higher presence of Native American and African MPA haplotypes in the region. Also of interest could be the presence of Asian MPA associations in this part of the megalopolis.

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## Supplemental Table S1.

Go to the following link for Supplementary Table S1: http://digitalcommons.wayne.edu/cgi/viewcontent.cgi?filename=0&article=1120&context=humbiol_preprints&type=additional.