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Genetic Differentiation in Mexico City Detected by HLA System Analysis

KEY WORDS: HLA, IMMUNOGENETICS, MEXICO CITY, ADMIXED POPULATIONS, TRANSPLANTATION, GENETIC POPULATION SUBSTRUCTURE

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 PCR-SSP procedures. Allelic and haplotypic frequencies, as well as population genetics parameters, were obtained by maximum likelihood methods. The most frequent haplotypes found included 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. Important to observe is that 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 it is commonly encountered in Native American human groups, which can be a

reflection on 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 haplotypic 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.

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 a intra- and inter-population 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 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), have been performed.

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 a relatively uniform genetics entity with Native American (50-60 %), European (25-40 %), African (4-12 %), and Asian (1 %) ancestral proportions (Lisker *et al*. 1990; Barquera *et al*. 2008; Juárez *et al*. 2008; Zúñiga *et al*. 2013; Ruíz-Linares *et al*., 2014). Little is known about the distribution of these HLA blocks in the mixed ancestry populations. Currently, there are no studies reporting phenomena related to genetic structure in urban settlements using HLA system as a genetic estimator. These studies would be useful for better organizing suitable stem cell donor banks, 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 *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 approx. 4.5 million. The type of industrialization together with economic development and rural migration contributed to the accelerated urban growth during this time (Aguilar & 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 with Mexico City´s northern city boundaries: between 1950 and 1980 the population living in those municipalities grew from approx. 233 000 to over 5 million people (Cervantes 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 into 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 & Mateos 2011) according to a selection of weighted median values of socioeconomic stratification classifier variables (Ruvalcaba & 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

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 (in terms of minimal wage[a]: less than five minimal wages, and for clusters 1 and 3, less than one) and a high incidence of migrants from other states into this region (Aguilar & 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 its effects in the analysis of alleles and associations relevant to the evaluation of the probability of 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 off 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*, IMSS) gave informed consent to participate in the study and were selected accordingly to their place of origin. Only non-genetically related individuals living in the mayoralties of the northern part of Mexico City and the municipalities of the State of Mexico belonging to the MAMC (mayoralties: Azcapotzalco, Gustavo A. Madero and Iztacalco, and municipalities: Naucalpan, Tlalnepantla, Ecatepec, Coacalco, Cuautitlán, Atizapán, and Tultitlán; Cervantes 1988) were selected.

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*, *-DRB1*, and *-DQB1* genes were genotyped by PCR-SSP (Polymerase chain reaction-Sequence specific primers) 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 ASHI (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 that have identical nucleotide sequences across the exons encoding the peptide binding domains (exon 2 and 3 for HLA class I and exon 2 for HLA class II alleles), were designated by an upper case 'G' following the fields of the allele designation of the lowest numbered allele in the group. HLA alleles having nucleotide sequences that encode the same protein sequence for the peptide

binding domains (exon 2 and 3 for HLA class I and exon 2 only for HLA class II alleles) were designated by an upper case 'P' which follows the allele designation of the lowest numbered allele in the group.

Statistical Analysis. Allelic and haplotypic frequencies were obtained by direct counting. Haplotypes were analyzed by maximum likelihood methods using the software *Arlequin* ver. 3.0 (Excoffier *et al*. 2007). This software was also used to calculate the observed (OH) and expected (EH) heterozygosity, as well as the Hardy-Weinberg equilibrium (HWE), using 1 x 10^6 dememorization steps. Values of $p < 0.05$ were considered as indicative of statistically significant differences between OH and EH and thus a deviation from HWE. Delta and standardized delta values used to measure LD were also calculated with *Arlequin* software. Standardized delta (Δ') values as a measurement of LD were estimated by previously described methods (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; Yunis *et al*. 2005).

Due to the fact that LD values may be the result of random associations between two infrequent alleles, our data was validated with the use of the statistic parameter *t* to adjust values by sample size and number of times that each allele appears in the sample (Haseman & 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 the reader is referred to Supplementary Table 1) and the frequencies (González Galarza *et al*. 2015) of 48 alleles of *HLA-B* and *HLA-DRB1* genes were used to graphically differentiate clusters by principal components analysis (PCA) using the software *SPSS Statistics* ver. 19 (*IBM Corporation,* Armonk, NY, USA) (Zúñiga *et al*. 2013).

Ancestral contribution proportions were estimated from the frequencies of haplotypes arranged by their 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 maximum likelihood (ML) method implemented in *LEADMIX* (Wang 2003), with $k = 3$ parental populations (African, American, and European) and *HLA-B* frequencies of 47 alleles as genetic estimator. The European contribution was estimated from a pooled sample (N = 1439) 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* (DKMS) donor registry of Germany (Pingel *et al*. 2013), Portuguese from northern, central and southern Portugal (Spínola *et al*. 2002) and northern Italian from Bergamo (Ferrara *et al*. 1998). The African component that was brought into the Americas due to slave trade during the colonial period (centuries 16^{th}-18^{th}; reviewed in Barquera & Acuña-Alonzo, 2012) was modeled with a pooled sample (N = 1236) 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 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), 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 is different to previous reports from Mexico City (Barquera *et al*. 2008, Zúñiga *et al*. 2013), the exact test of genetic differentiation based on the frequency of haplotypes (Rousset & Raymond 1995; Goudet *et al*, 1996) as implemented in *Arlequin* software ver. 3.0 (Excoffier *et al*. 2007) with 3 x 10^6 steps in the Markov chain was used.

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 alleles of *HLA-A*, 41 alleles of *HLA-B*, 15 alleles of *HLA-DRB1*, and seven *HLA-DQB1* 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*/*-DRB1*/*-DQB1* haplotypes were found in the northern Mexico City sample set. The analysis of two-point associations between *HLA-A*/*-B*, *HLA-B*/*-DRB1*, and *HLA-DRB1*/*-DQB1*and their statistical parameters are shown in Tables 2-4. Twelve *HLA-A*/*-B* associations showed statistical significance accordingly to *t* value; however, only eight were present in HF > 1.0 % (Table 2). Eleven out of 13 *HLA-B*/*-DRB1* blocks with statistically significant *t* values were present in HF > 1.0 % (Table 3). All twelve class II associations with statistically significant *t* values were found in 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 proportions: 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 a 42.44% European component, 3.62% African contribution and a 53.95% Native American component.

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 when compared to previous reports from Mexico City (Figure 3). The exact test of genetic differentiation based on the frequency of haplotypes further demonstrated that the three samples from Mexico City analyzed were statistically different from each other ($p < 0.0001$).

Discussion

Even though no significant differences were found regarding the ML admixture estimations between our sample and previous reports, it is noticeable that haplotypic diversity is more informative than allele-based admixture estimation. When 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 in comparison to European ones. This tendency can be a result of the 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 %; INEGI 2011, Figure 1). Moreover, previous reports (Barquera *et al*. 2008, Zúñiga *et al*. 2013) examining Mexico City were shown to be 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 report (to the authors' knowledge) 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). Important to observe is that 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 these 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 Chinese, Japanese and Korean migrations due to the changes in foreign affairs laws and policies during the 19th century and the beginning of the 20th century

encouraging the settlement and naturalization of foreigners including integration into economic activities (Acosta & Zizumbo 2011; Romero 2000).

Mixed ancestry haplotypes can arise from the complex population dynamics present in this region for over 500 years. Blocks with Native 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 are indicative of 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 of not only haplotypes with distinct probable ancestries, but of new haplotypes that may only be found in other populations sharing a similar demographic history. Updates in the datasets of potential hematopoietic cell donors, cadaveric donor programs, and panel reactive antibodies (PRA) analysis is needed to incorporate these mixed ancestry phenotypes to better provide the biomedical research community with appropriate results.

When all information is taken into consideration, it appears that the conclusions drawn from samples from Mexico City as a homogeneous conglomerate (Lisker *et al*. 1990; Barquera *et al*. 2008; Juárez *et al*. 2008; Zúñiga *et al*. 2013; Ruíz-Linares *et al*., 2014) cannot be extrapolated to the distinct social, economic and geographic regions in which the megalopolis is divided into. 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 2010).

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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Table 1. Allelic frequencies of the genes *HLA-A, -B, -DRB1*, and *-DQB1* in a northern Mexico City sample set.

HLA-A	**A.F.**	**N = 344 n**	***HLA-B***	**A.F.**	**N = 344 n**	***HLA-DRB1***	**A.F.**	**N = 344 n**	***HLA-DQB1***	**A.F.**	**N = 344 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						

A.F.: Allelic frequency.

Table 2. *HLA-A/-B* most frequent associations in a northern Mexico City sample set.

HLA-A/-B	**H.F.**	**N = 344** **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

Values in bold indicate statistic significance ($p < 0.05$; $t \geq 2$). Shaded rows correspond to statistic significance for both *p* and *t* values. H.F.: Haplotypic frequency; |Δ'|: Absolute value of standardized LD. *p*: statistical significance; *t*: validation statistic.

Table 3. *HLA-B/-DRB1* most frequent associations in a northern Mexico City sample set.

HLA-B/-DRB1	**H.F.**	**N = 344** **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**

Values in bold indicate statistic significance ($p < 0.05$; $t \geq 2$). Shaded rows correspond to statistic significance for both *p* and *t* values. H.F.: Haplotypic frequency; |Δ'|: Absolute value of standardized LD. *p*: statistical significance; *t*: validation statistic.

Table 4. *HLA-DRB1/-DQB1* most frequent associations in a northern Mexico City sample set.

HLA-DRB1/-DQB1	**H.F.**	**N = 344** **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

Values in bold indicate statistic significance ($p < 0.05$; $t \geq 2$). Shaded rows correspond to statistic significance for both *p* and *t* values. H.F.: Haplotypic frequency; |Δ'|: Absolute value of standardized LD. *p*: statistical significance; *t*: validation statistic.

Table 5. *HLA-A/-B/-DRB1/-DQB1* most frequent haplotypes (H.F. > 0.01) in a sample set of northern Mexico City and reports in previous populations.

Haplotype				N = 344					Previously reported in: Population (Ref.) frequency.
				H.F.	n	|Δ'|	*p*	*t*	
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 et al. 2000) 0.149; Maya (Gómez et al. 2003) 0.042; Teenek (Vargas 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 et al. 2003) 0.155; Maya (Gómez et al. 2003) 0.106; Uro (Arnaiz et al. 2009) 0.063; Mixtec (Hollenbach et al. 2001) 0.030; Mazatec (Arnaiz et al. 2000) 0.025; Nahua (Vargas 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 et al. 2003) 0.064; Teenek (Vargas 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 et al. 2009) 0.168; Aymara (Arnaiz et al. 2005) 0.104; Mixtec (Hollenbach et al. 2001) 0.090; Maya (Gómez et al. 2003) 0.084; Mexico City (Zúñiga et al. 2013) 0.037; Tarahumara (García 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 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 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 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 et al. 2009) 0.068; Yup'ik (Moscoso et al. 2006) 0.06; Mixtec (Hollenbach et al. 2001) 0.050; Maya (Gómez et al. 2003) 0.042; Aymara (Arnaiz 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 et al. 2001) 0.049; Poland (Nowak et al. 2008) 0.040; Basques (Sánchez 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 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 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 et al. 2006) 0.034; Costa Rica Central Valley (Arrieta et al. 2011) 0.019; "Hispanic" (Maiers et al. 2007) 0.001.

Values in bold indicate statistical significance ($p < 0.05$; $t \geq 2$). Shaded rows correspond to statistical significance for both *p* and *t* values. H.F.: Haplotypic frequency; |Δ'|: Absolute value of standardized LD. *p*: statistical significance; *t*: validation statistic.

Figure 1. A) Mexico City's urban extent in 1950 (red). **B)** Mexico City's urban extent in 1970 (red). **C)** Mexico City's current urban footprint in 2014 (red corresponds to 1970 urban extent and orange corresponds to current 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 colored in light green, whereas pink-colored states represent the region of northern Mexico City Metropolitan Area where they principally settle (Aguilar & Mateos 2011). Blue-shaded sections in Figures 1A-1C correspond to administrative boundaries of present day Mexico City. Maps are modified from *Google Earth* (Google Inc. 2010) and *Story Maps. The Age of Megacities* (ESRI 2014).

Figure 2. Haplotypic contributions of MPA found in a sample from northern Mexico City. NatAm: Native American; Eur: European; Asi: Asian; Afr: African; No rep: Not previously reported; Mix: Mixed ancestry.

Figure 3. Principal components analysis (PCA) plot of 78 populations and 48 HLA-B and HLA-DRB1 alleles. European populations are represented by green dots; African human groups correspond to yellow dots; red dots were assigned to Asian populations; Native American populations are represented by purple dots; Admixed populations are indicated with blue dots. Our northern Mexico City sample is represented by a blue star. 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: Jordania, Mad: Madeira, Mal: Malasya, 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: Perú (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.

Figure 1.

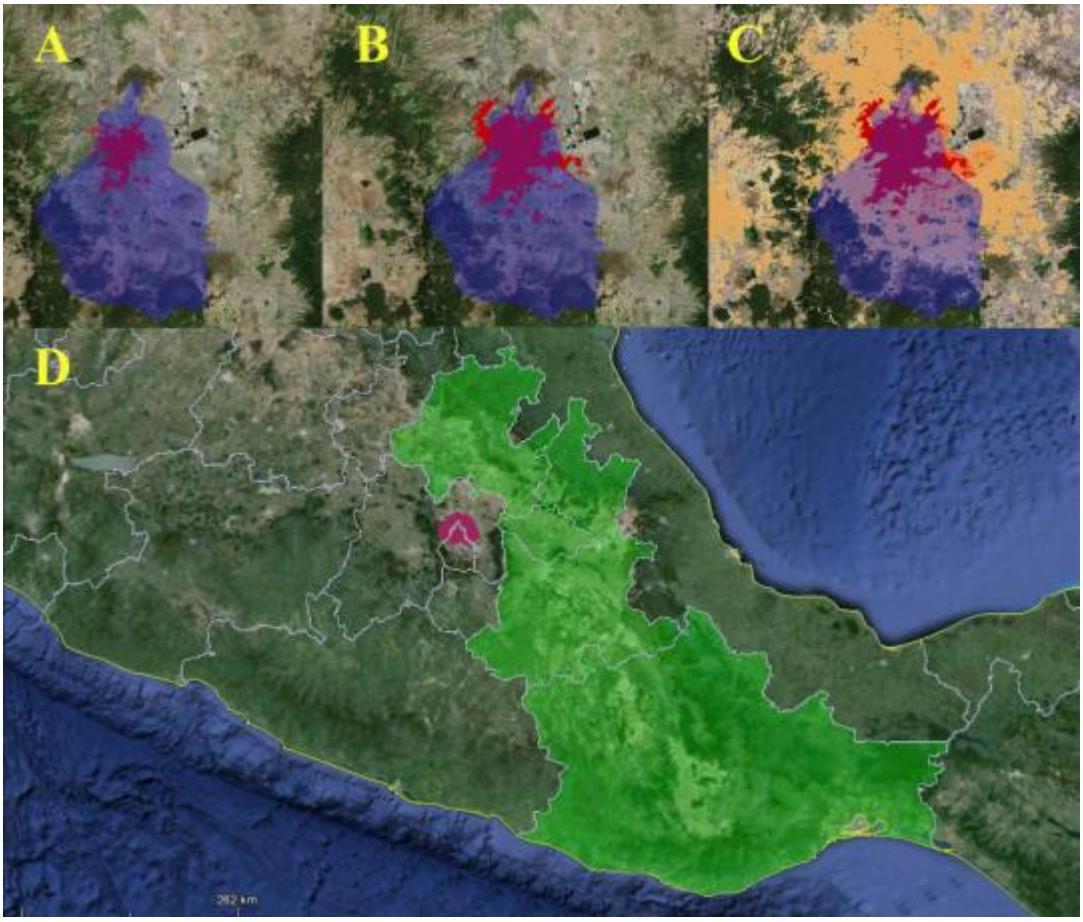

Figure 2.

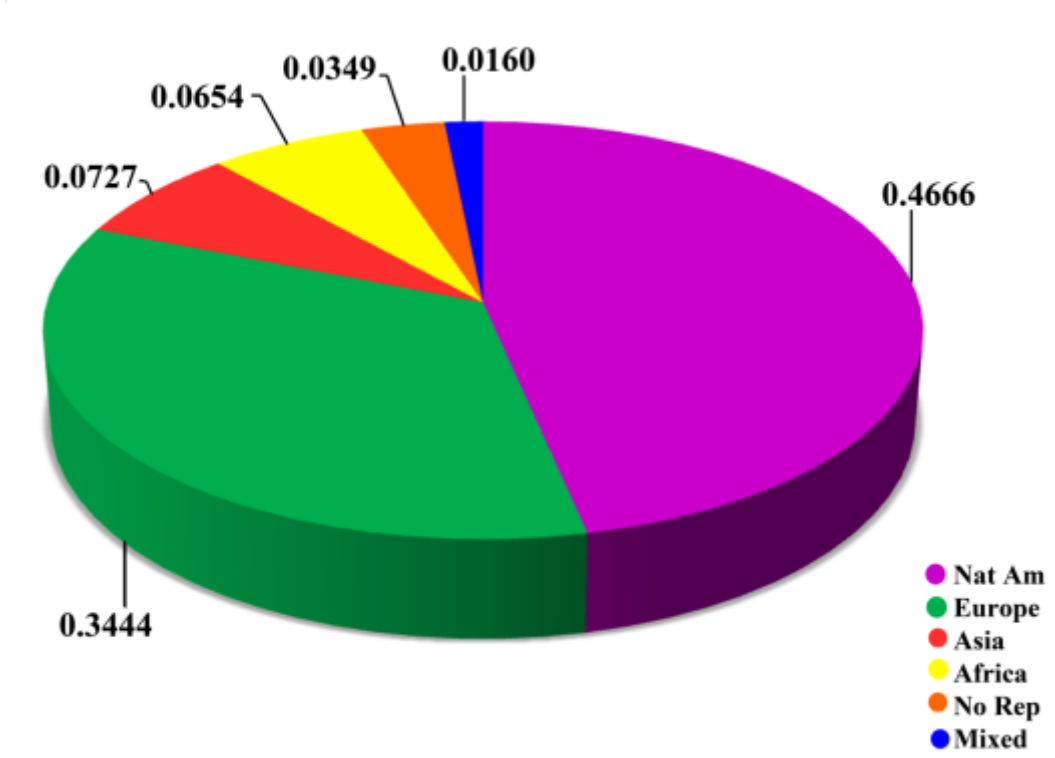

Figure 3.