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Research article

The immunogenetic diversity of the HLA system in Mexico correlates with underlying population genetic structure

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Abbreviations: HLA, Human Leukocyte Antigen; MPA, Most-probable ancestry; LD, Linkage Disequilibrium

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ABSTRACT

We studied HLA class I (*HLA-A*, *-B*) and class II (*HLA-DRB1*, *-DQB1*) allele groups and alleles by PCR-SSP based typing in a total of 15,318 mixed ancestry Mexicans from all the states of the country divided into 78 sample sets, providing information regarding allelic and haplotypic frequencies and their linkage disequilibrium, as well as admixture estimates and genetic substructure. We identified the presence of 4268 unique HLA extended haplotypes across Mexico and find that the ten most frequent (HF > 1%) HLA haplotypes with significant linkage disequilibrium ($\Delta' \geq 0.1$) in Mexico (accounting for 20% of the haplotypic diversity of the country) are of primarily Native American ancestry (A*02∼B*39∼DRB1*04∼DQB1*03:02, A*02∼B*35∼DRB1*08∼DQB1*04, A*68∼B*39∼DRB1*04∼DQB1*03:02, A*02∼B*35∼DRB1*04∼DQB1*03:02, A*24∼B*39∼DRB1*14∼DQB1*03:01, A*24∼B*35∼DRB1*04∼DQB1*03:02, A*24∼B*39∼DRB1*04∼DQB1*03:02, A*02∼B*40:02∼DRB1*04∼DQB1*03:02, A*68∼B*35∼DRB1*04∼DQB1*03:02, A*02∼B*15:01∼DRB1*04∼DQB1*03:02). Admixture estimates obtained by a maximum likelihood method using *HLA-A/-B/-DRB1* as genetic estimators revealed that the main genetic components in Mexico as a whole are Native American (ranging from 37.8% in the northern part of the country to 81.5% in the southeastern region) and European (ranging from 11.5% in the southeast to 62.6% in northern Mexico). African admixture ranged from 0.0 to 12.7% not following any specific pattern. We were able to detect three major immunogenetic clusters correlating with genetic diversity and differential admixture within Mexico: North, Central and Southeast, which is in accordance with previous reports using genome-wide data. Our findings provide insights into the population immunogenetic substructure of the whole country and add to the knowledge of mixed ancestry Latin American population genetics, important for disease association studies, detection of demographic signatures on population variation and improved allocation of public health resources.

1. Introduction

The biological diversity exhibited by modern Latin American populations is rooted in the demographic history (a process of extensive geographic and social stratification) of the human groups that constitute their biological ancestries. Previous studies [1,2] have shown that the geographic distribution of admixture proportions reveals extensive population structure, depicting the continuing impact of

Table 1
Analytical units for the Mexican mixed ancestry populations studied in this work.

Region	State	Analytical Unit	IPD-IMGT/HLA [1 0 2} Database versions used	Population	N =	AFDN-ID [REF.]
Northwestern	Baja California (BC)	1	3.5.0 – 3.25.0	Baja California La Paz	75	AFDN-ID: 3526 [67]
				Baja California Mexicali	100	AFDN-ID: 3527 [67]
				Baja California Tijuana	25	AFDN-ID: 3615 [67]
				Baja California Rural	50	AFND-ID: 3571 [67]
	Sonora (Son)	2	3.5.0 – 3.10.0	Sonora Hermosillo	99	AFND-ID: 3523 [68]
				Sonora Ciudad Obregón	143	AFND-ID: 3524 [68]
				Sonora Rural	197	AFND-ID: 3572 [68]
	Sinaloa (Sin)	3	3.5.0 – 3.10.0	Sinaloa Culiacan	103	AFND-ID: 3521 [79]
				Sinaloa Rural	183	AFND-ID: 3573 [79]
	Chihuahua (Chi)	4	3.3.0 – 3.25.0	Chihuahua city	119	AFND-ID: 3519 [90]
				Ciudad Juárez	106	AFND-ID: 3518 [90]
				Chihuahua Rural	236	AFND-ID: 3574 [90]
	Durango (Dur)	5	3.3.0 – 3.25.0	Durango city	153	AFND-ID: 3516 [91]
				Durango Rural	326	AFND-ID: 3575 [91]
Northeastern	Coahuila (Coa)	6	3.3.0 – 3.25.0	Coahuila Torreón	396	AFND-ID: 3513 [92]
				Coahuila Saltillo	72	AFND-ID: 3514 [92]
				Coahuila Rural	216	AFND-ID: 3576 [92]
	Zacatecas (Zac)	7	3.3.0 – 3.25.0	Zacatecas city	84	AFND-ID: 3511 [93]
				Zacatecas Fresnillo	103	AFND-ID: 3510 [93]
				Zacatecas Rural	266	AFND-ID: 3577 [93]
	Aguascalientes (Ags)	8	3.3.0 – 3.25.0	Aguascalientes	95	AFND-ID: 3493 [72]
	Nuevo León (NL)	9		Nuevo León Monterrey	226	AFND-ID: 3494 [71]
				Nuevo León Rural	439	AFND-ID: 3583 [71]
	Tamaulipas (Tam)	10	3.3.0 – 3.25.0	Tamaulipas Ciudad Victoria	23	AFND-ID: 3489 [74]
				Tamaulipas Rural	125	AFND-ID: 3585 [74]
	San Luis Potosí (SLP)	11	3.3.0 – 3.25.0	San Luis Potosí city	30	AFND-ID: 3487 [75]
				San Luis Potosí Rural	87	AFND-ID: 3586 [75]
Western	Nayarit (Nay)	12	3.8.0 – 3.19.0	Nayarit Tepic	97	AFND-ID: 3508 [94]
				Nayarit Rural	64	AFND-ID: 3578 [94]
	Jalisco (Jal)	13	3.3.0 – 3.25.0	Jalisco Guadalajara	1189	AFND-ID: 3506 [95]
				Jalisco Rural	585	AFND-ID: 3579 [95]
				Jalisco Tlajomulco	30	AFND-ID: 3505 [95]
				Jalisco Tlaquepaque	39	AFND-ID: 3504 [95]
				Jalisco Tonalá	35	AFND-ID: 3503 [95]
				Jalisco Zapopan	168	AFND-ID: 3502 [95]
	Michoacán (Mic)	14	3.3.0 – 3.25.0	Michoacán Morelia	150	AFND-ID: 3500 [96]
				Michoacán Rural	348	AFND-ID: 3580 [96]
	Guanajuato (Gua)	15	3.11.0 – 3.15.0	Guanajuato city	22	AFND-ID: 3498 [69]
				Guanajuato León	78	AFND-ID: 3497 [69]
				Guanajuato Rural	162	AFND-ID: 3581 [69]
	Colima (Col)	16	3.8.0 – 3.19.0	Colima city	61	AFND-ID: 3496 [70]
				Colima Rural	43	AFND-ID: 3482 [70]
Center	Queretaro (Que)	17	3.3.0 – 3.25.0	Querétaro city	45	AFND-ID: 3491 [73]
				Querétaro Rural	43	AFND-ID: 3584 [73]
	Veracruz (Ver)	18	3.3.0 – 3.25.0	Veracruz Xalapa	187	AFND-ID: 3480 [76]
				Veracruz city	171	AFND-ID: 3481 [76]
				Veracruz Coatzacoalcos	55	AFND-ID: 3485 [76]
				Veracruz Córdoba	56	AFND-ID: 3483 [76]
				Veracruz Poza Rica	45	AFND-ID: 3482 [76]
				Veracruz Orizaba	60	AFND-ID: 3484 [76]
				Veracruz Rural	539	AFND-ID: 3587 [76]
	Hidalgo (Hid)	19	3.3.0 – 3.25.0	Hidalgo Pachuca	41	AFND-ID: 3478 [89]
				Hidalgo Rural	81	AFND-ID: 3588 [89]
	Mexico City (CDMX)	20	3.3.0 – 3.25.0	Mexico City North	751	AFND-ID: 3474 [77]
				Mexico City Center	152	AFND-ID: 3476 [77]
				Mexico City South	52	AFND-ID: 3473 [77]
				Mexico City East	79	AFND-ID: 3475 [77]
				Mexico City West	33	AFND-ID: 3454 [77]
				Mexico City Rural	150	AFND-ID: 3589 [77]
	Tlaxcala (Tla)	21	3.3.0 – 3.14.0	Tlaxcala city	181	AFND-ID: 3471 [78]
				Tlaxcala Rural	830	AFND-ID: 3590 [78]
	Puebla (Pue)	22	3.3.0 – 3.14.0	Puebla city	1994	AFND-ID: 3469 [80]
				Puebla Rural	833	AFND-ID: 3591 [80]
	Guerrero (Gue)	23		Guerrero	144	AFND-ID: 3468 [81]
	Oaxaca (Oax)	24	3.3.0 – 3.14.0	Oaxaca city	151	AFND-ID: 3466 [82]
				Oaxaca Rural	485	AFND-ID: 3592 [82]
	Morelos (Mor)	25	3.3.0 – 3.25.0	Morelos Cuernavaca	82	AFND-ID: 3464 [83]
				Morelos Rural	30	AFND-ID: 3593 [83]

(*continued on next page*)

Table 1 (*continued*)

Region	State	Analytical Unit	IPD-IMGT/HLA [1 0 2] Database versions used	Population	N =	AFDN-ID [REF.]
Southeastern	Tabasco (Tab)	26	3.3.0 – 3.13.0	Tabasco Villahermosa	82	AFND-ID: 3462 [84]
				Tabasco Rural	142	AFND-ID: 3572 [84]
	Chiapas (Cha)	27	3.3.0 – 3.13.0	Chiapas Tuxtla Gutiérrez	52	AFND-ID: 3460 [85]
				Chiapas Rural	121	AFND-ID: 3595 [85]
	Campeche (Cam)	28	3.3.0 – 3.13.0	Campeche city	34	AFND-ID: 3458 [86]
				Campeche Rural	47	AFND-ID: 3596 [86]
	Yucatán (Yuc)	29	3.3.0 – 3.13.0	Yucatán Mérida	192	AFND-ID: 3456 [87]
				Yucatán Rural	132	AFND-ID: 3597 [87]
	Quintana Roo (QRo)	30	3.3.0 – 3.25.0	Quintana Roo Cancún	48	AFND-ID: 3450 [88]
				Quintana Roo Rural	50	AFND-ID: 3598 [88]

AFND-ID: Allele Frequencies Net Database Identifier. “Baja California” includes both Baja California Norte and Baja California Sur. “Mexico City” includes both Mexico City and the State of Mexico.

demographic history on the genetic diversity of Latin America at a genomic level. The human groups giving rise to present day Latin American mixed ancestry populations include Native Americans living in distinct environments [3–10] and with different genetic backgrounds [2,11–16]; Europeans, mainly from Iberia [17,18]; genetically and culturally diverse enslaved sub-Saharan Africans [19–23]; unknown numbers of other ethnic groups and minorities such as North Africans, Middle Easterners and Romani [24]; and Asian migrants mainly from South East Asia [25,26]. All these populations started to arrive and/or to be assimilated into mixed-ancestry societies throughout the colonial period [24,25] and have continued to do so with different intensities and flow dynamics until the present day [27,28]. Acknowledging this biological diversity, and its underlying genetic structure, is central for understanding regional variation and the impact of such variation on clinical and biomedical interventions [13]. Of special interest is the Human Leukocyte Antigen (HLA) genetic system, due to its importance in several clinical interventions such as matching transplant donors and recipients [29], autoimmunity [30] and drug-induced hypersensitivity [31,32].

The diversity of HLA illustrates inclusive fitness [33–35], with clear differences among human groups with regards to the frequencies of HLA alleles and haplotypes [36–44]. This represents a challenge for both solid organ and hematopoietic stem cell (HSC) transplantation procedures [45–49], in particular in mixed-ancestry human groups, which is the case for Mexico and Latin America. In these populations, the presence of ancestry-specific haplotypes of different origins in the same patient, or patients having one mixed-ancestry haplotype, can significantly complicate the search for optimal donors (reviewed in [50]).

The aim of the present work is to assess the diversity and distribution of HLA allele groups and haplotypes in Mexico, and to identify the regions in which immunogenetic substructure arises as a result of differences in the demographic histories of cities, states or regions of the country. Our work provides results important for disease association studies, detection of demographic signatures on population variation, and a better allocation of public health resources, hence providing medical and clinical teams with data sufficient to better distribute the biological resources in benefit of their patients [39].

2. Subjects, materials and methods

The materials and methods here described are also the same for the Short Population Reports (SPR) [51] for each population sample set presented in this issue [52–81], except where otherwise stated. Further information can be found in the Supplementary Material.

2.1. Subjects

Peripheral blood was obtained by venipuncture from 15,318 non-related mixed ancestry Mexicans living in all states of Mexico (please refer to the *Supplementary Information*. *Material and Methods* section for further information). Subjects self-described as mixed ancestry (i.e. *Mestizo*) in the questionnaires used for either clinical records or as part of the sampling procedures for the research protocols. The collection of blood samples was performed according to the requisites of the Helsinki Declaration (2008) and the General Health Law of Mexico. All subjects or their legal representatives were informed about the objectives and methods used, and signed an informed consent form. To avoid potential bias, participants with any HLA-associated clinical condition or cancer [30,82]) were excluded. Previous studies have shown no statistically significant differences in HLA allele frequencies between patients and organ donors when these conditions are used as exclusion criteria [83]. We considered 78 discrete sample sets (average number of haplotypes per analytical unit: 2 N = 196.4) conforming 30 analytic units (Table 1). Each analytical unit (either a state or the combination of two states) is a sum of the individual genotypes of the populations comprised in that analytical unit (usually, cities and rural areas). All data for each of the populations is held in www.allelefrequencies.net (AFND) [36] under the ID numbers given in Table 1. However, data at the state level is not held in AFND to prevent duplication of frequency data. All unrelated individuals are Mexicans by birth and have permanent residence within the country [84]. To the best of our knowledge, no individuals whose samples were included as part of the final dataset were related but it would be impossible to completely exclude that possibility. The use of renal recipients could have introduced a very small bias due to HLA association with diseases leading to renal failure, but by excluding autoimmune conditions known to be associated with HLA we tried our best to control such bias.

2.2. HLA typing

Briefly, genomic DNA was extracted from peripheral blood using standardized procedures (*DNA Isolation Kit for Mammalian Blood*, Roche Diagnostics, Basel, Switzerland; automated DNA extraction with the *MagNA Pure Compact System*, Roche Molecular Systems, Pleasanton, CA, USA; in-house validated salting out techniques), and DNA was adjusted to a final concentration of 80–120 ng/μL and stored at –20 °C until use. HLA genotyping was performed with two different approaches: either using commercially available PCR sequence-specific primers (PCR-SSP) kits (*AB/DR/DQ SSP Unitray®*, Life Technologies/Thermo Fisher Scientific Inc., Waltham, MA, USA; *SSP Combi trays*, *Olerup SSP AB*, Stockholm, Sweden; *HLA-Ready Gene ABC/DRDQDP plus*, inno-train Diagnostik GmbH, Kronberg, Germany) under ASHI requirements [85] or by allele imputation from SNP data [86]. For the first strategy (N = 15,175), PCR products were loaded onto a 2% agarose gel for electrophoresis. Finally, the ethidium bromide-stained gel was photographed and the band pattern analyzed with either *UniMatch™ Plus* software (Life Technologies/Thermo Fisher Scientific Inc.) or *Score™* software (*Olerup SSP AB*, Stockholm, Sweden) using up-to-date versions (at the time of the genotyping; ver. 3.3.0 – ver. 3.25.0) of the IPD-

IMGT/HLA Database [87] (Table 1). All HLA typing centers performed the genotyping under ASHI requirements [85] with a procedure validated using an external quality control program (the UCLA International HLA DNA Exchange program). To keep data consistent, all typings were checked before their inclusion in the final dataset.

The data analyzed are heterogeneous in terms of resolution with a mix of one-field (allelic groups) and two-field (alleles) names for the *HLA-B*, *-DRB1* and *-DQB1* loci, and only one-field names for the *HLA-A* locus. HLA typings with broad antigens (i.e. those that can be subdivided into split antigens such as HLA-B15) were further analyzed with a high-resolution PCR-SSP kit (*SSP Unitray Direct To High-Resolution HLA-B*, *-DRB*, Life Technologies/Thermo Fisher Scientific Inc.; *AllSet™ Gold HLA-B High Res*, Life Technologies/Thermo Fisher Scientific Inc.; DRB1 SSP Unitray®, Invitrogen/Life Technologies/Thermo Fisher Scientific Inc.; or *-DQB1* SSP *Unitray®*, Life Technologies/Thermo Fisher Scientific Inc.). All alleles were classified accordingly to the WHO Nomenclature Committee for Factors of the HLA System [88,89], using up-to-date versions (at the time of the genotyping; ver. 3.3.0 - ver. 3.25.0) of the IPD-IMGT/HLA Database [87]. In compliance with ASHI requirements [85], whenever a HLA typing at one field remained unsolved after studying the complete family, or when a homozygous typing was obtained, sequence-based typing was performed to correctly assign the allele either at the Histocompatibility Laboratory, Central Blood Bank, Centro Médico Nacional "La Raza", or at Laboratorios Diagnomol, both in Mexico City, with a procedure validated using an external quality control program (the UCLA International HLA DNA Exchange program). This was the case for 886 individuals. No new alleles were detected.

2.3. Statistical analysis

2.3.1. HLA allelic and haplotypic diversity

Observed heterozygosity (OH) and expected heterozygosity (EH) at a locus-by-locus level, Hardy–Weinberg equilibrium (HWE) and maximum-likelihood (ML) frequencies for allele groups and alleles and four-locus haplotypes were estimated using an Expectation-Maximization (EM) algorithm provided by the computer program *Arlequin* ver. 3.5 [90]. For a total of 30,636 haplotypes, 96.05% of them were phased by family segregation and ML was used for 3.95%. Linkage disequilibrium (LD; Δ and Δ′) were also calculated using *Arlequin* [42,84,90]. Haplotypes of Native American, African, Asian, and European most-probable ancestry (MPA) were assigned based on known allele group, allele and haplotype frequency distributions in worldwide populations, geographic origin of cell lines used to describe specific alleles and highly conserved geographic-specific linkages for HLA haplotypes [36,42,43,87,91–95]. We then used each locus in the extended haplotype to evaluate the presence of population-specific alleles or allele groups (i.e., alleles or allele groups which are exclusively found in a specific non-recently admixed human continental group or that are very rare in other continental human groups [93]).

Because many associations may return Δ′ values of 1.000 even though that value may result from a random association between two infrequent alleles, we used a statistical parameter, *t*, to validate all Δ′ data adjusted by the sample size and number of times that each allele appeared in the sample [84,96]. For each pair of alleles (or blocks), *t* was calculated as follows:

$$t = \frac{2N\Delta_{ij}}{\sqrt{a - 4N\Delta_{ij}\left(\frac{B+D}{2\sqrt{BD}} - \frac{\sqrt{BD}}{N}\right)}}$$

where N = the total number of gametes; Δ_{ij} = LD value of the *i–j* allele association, *i* is an allele of the gene *X*, and *j* an allele of the gene *Y*; *a* = the number of times that *i* and *j* alleles appeared together in the sample; *B* = absolute frequency of non-*i* alleles; and *D* = the absolute frequency of non-*j* alleles. Only *t* values ≥ 2 were taken as statistically significant within this population context.

2.3.2. Admixture proportions calculations

To further test the fitness of HLA-based admixture estimates we used the ML method and *LEADMIX* software [97], with $k = 3$ parental populations (African, Native American and European) and three different strategies: *HLA-B*, *HLA-B/-DRB1* or *HLA-A/-B/-DRB1* allele groups and allelic frequencies as admixture estimators. HLA admixture estimates were contrasted against whole-genome admixture estimates with a comparison of proportion test [98,99] with *p* values corrected for multiple comparisons using the Bonferroni correction (*k* comparisons; $k = 2$ for *HLA-B/-DRB1* and $k = 3$ for *HLA-A/-B/-DRB1*) [100]. After assessing which would be the best combination to better estimate admixture proportions, the resulting strategy (*HLA-A/-B/-DRB1*) was used to estimate ancestral contributions in the 30 analytical units and their corresponding populations, analyzed in this work.

2.3.3. Genetic diversity and genetic substructure assessment

For the genetic diversity analyses, we reduced the typing resolution of all populations to one-field resolution for consistency. To plot the relationships among mixed-ancestry Mexican populations and their relationships with other human groups, linear combinations were obtained from a matrix of 287 populations, including the Mexican groups analyzed in this work as well as 33 Native American groups, 52 Asian groups, 12 North African groups, 23 Sub-Saharan African groups, 16 Oceanian groups and 40 European groups (please refer to Supplementary Table 1 for further information). Based on previous reports [101,102], forty-eight *HLA-B* and *HLA-DRB1* allele group frequencies were used to separate clusters with principal component analysis (PCA) using *IBM SPSS Statistics 19* Software (IBM Corp., Armonk, NY, USA). To further confirm the areas where a given variable shows an abrupt rate of change (i.e. genetic barriers) among mixed ancestry Mexican groups, we used the software *Barrier* ver. 2.2 [103] using D_{ST} values calculated with *POPTREEW* [104]. D_{ST} distance measures were computed from *HLA-B* and *HLA-DRB1* frequency data from each Mexican sample set using sample size bias correction [105,106]. The phylogeny was modeled under a neighbor-joining (NJ) model and using bootstrapping with 1250 replications. We used the exact test of sample differentiation based on haplotype frequencies and genetic distances obtained by pairwise differences between haplotypes for each population to statistically demonstrate the differences between each pair of Mexican sample datasets. Using these distances we constructed a matrix (product of 110 permutations) of significant F_{ST} *p* values using *Arlequin* software ver. 3.11 [107–109] with a significance level of 0.05. To assess genetic diversity [84] of all the sample sets, polymorphism information content (PIC) and power of discrimination (PD) [110–112] were calculated using the *PowerStat* ver. 1.2 spreadsheet (Promega Corporation, Fitchburg, WI, USA). A value of PIC > 0.5 is considered to be characteristic of highly polymorphic systems, and a PD value > 0.8 indicates high polymorphism in a specific population context [84,110–112].

3. Results

3.1. HLA allele groups

Eleven *HLA-A* allele groups were present in all states analyzed (Supplementary Table 2). The three most frequent *HLA-A* allele groups in Mexico (65% of total *HLA-A* variation in the sample set) are HLA-A*02 (33.92% in the whole country; ranging from ~ 20% in the southeastern regions to over 40% in the central region), A*24 (16.98% in the whole country; ranging from ~ 14% in the northwestern region to around 20% in the central and southeastern region) and A*68 (14.67% in the whole country; rising in frequency from the northwestern region with frequencies around 8% to over 20% in the southeastern region), all of which can be consistently found in relatively high frequencies [36] among Native American groups [41,113–121]. Sixteen *HLA-B* allele groups were present in all states analyzed (Supplementary

Table 3). The four most frequent allele groups and alleles for *HLA-B*, which represent over 50% of total *HLA-B* variation in the country, are HLA-B*35 (20.55% in the whole country; ranging from less than 19% in states from the northern and western parts of the country to over 24% in southeastern Mexico), B*39 (16.51% in the whole country; ranging from less than 10% in northern Mexico to > 20% in the southeastern part of the country), B*40:02 (7.72% in the whole country; with frequencies ranging from 4.62% to 12.35% without any specific distribution pattern) and B*51 (5.40% in the whole country; ranging from 2.47% to 8.17% being slightly more represented among states in the northern part of the country), all of which are also common in Native American groups [41,113–117,119–127]. Ten *HLA-DRB1* allele groups were present in all states analyzed (Supplementary Table 4). The four most frequent *HLA-DRB1* allele groups (> 60% of the total *HLA-DRB1* diversity in the sample set) are HLA-DRB1*04 (ranging from ~ 25% in the north western region to over 40% in the southeastern), DRB1*08 (frequencies ranging from 4.76% to around 20% in the central part of the country but without any specific pattern), DRB1*14 (going from 5.13% to 14.49%, without any specific pattern) and DRB1*07 (ranging from 3.41% to 10.71%, without any specific pattern). The first three are also frequently found in Native American populations [41,116,119,120,124,125,127–134]. HLA-DRB1*07 is commonly found in non-Native American populations such as Africans [135–138], Asians [139–141], and Europeans [142–145]. Six *HLA-DQB1* allele groups and alleles were present in all states analyzed (Supplementary Table 5). The three most frequent *HLA-DQB1* allele groups and alleles (DQB1*03:02, DQB1*03:01, and DQB1*04) retain over 68% of the diversity and follow the patterns observed for *HLA-DRB1* allele groups due to their strong LD.

3.2. Haplotypic diversity

We found a total of 4268 HLA extended haplotypes in the whole dataset. None of the haplotypes present in the analyzed sample sets had a frequency above 3.5% (Supplementary Table 6). The top 68 haplotypes represent roughly 50% of the haplotypic distribution, with the top 15 accounting for 25% of the haplotypic diversity in our sample set. Even though the vast majority of them are of Native American MPA, some European MPA haplotypes such as HLA-A*01~B*08~DRB1*03:01~DQB1*02 (0.95%, n = 291), HLA-A*29~B*44~DRB1*07~DQB1*02 (0.89%, n = 272), HLA-A*33~B*14:02~DRB1*01~DQB1*05 (0.75%, n = 228), HLA-A*03~B*07~DRB1*15~DQB1*06 (0.60%, n = 184), HLA-A*02~B*44~DRB1*07~DQB1*02 (0.47%, n = 143), and A*68~B*14:02~DRB1*01~DQB1*05 (0.45%, n = 139) are among the most frequently found in Mexican mixed-ancestry populations. These haplotypes have also been found in other mixed ancestry populations of Latin America [102,146,147], especially in those with a high prevalence of European ancestry [1,148–150].

Of note, the nine most frequent HLA haplotypes, all of which are of Native American MPA, account for roughly 20% of the haplotypic diversity of Mexican populations, and have been reported previously both in Native [41,93,113,118,120,124–127,129,132,151,152] and in mixed-ancestry populations from Latin America and the United States [84,93,94,101,102,146,150,153–158]. Notably, haplotype HLA-A*30~B*13~DRB1*07~DQB1*02, of Eurasian MPA [36], is present among the most frequent haplotypes of the country, with an overall frequency of 0.40% (n = 122) and reaching a peak in states from northern Mexico (Supplementary Table 6). For all the SPRs for each population sample set presented in this issue [52–81] we used the same criteria (H.F. > 1.0%, arbitrarily [92]).

3.3. Admixture estimates

The results for the comparisons between the HLA and whole genome admixture estimates are summarized in Supplementary Table 7 and in the Supplementary Methods section. The prevalence of Native American, European and African components is summarized in Fig. 1. Admixture estimates obtained by the ML method revealed that the main genetic components in Mexico as a whole are Native American (ranging from 37.8% in the northern part of the country to 81.5% in the southeastern region) and European, ranging from 11.5% in the southeast to 62.6% in northern Mexico, and having opposing prevalence along the northwest-southeast cline. The African component ranges from 0.0% to 12.7% throughout the entirety of the country but not following any specific pattern (Fig. 1). A graphic with admixture estimates for all the states analyzed can be found in Supplementary Figs. 1 and 2, and exact values can be found in each of the short population reports in this issue for the states, the cities and the rural areas.

3.4. Genetic diversity and genetic substructure assessment

For the PCA (Fig. 2 and Supplementary Fig. 3) we observe that PC1 (49.9% of the variance) scatters worldwide populations from East to

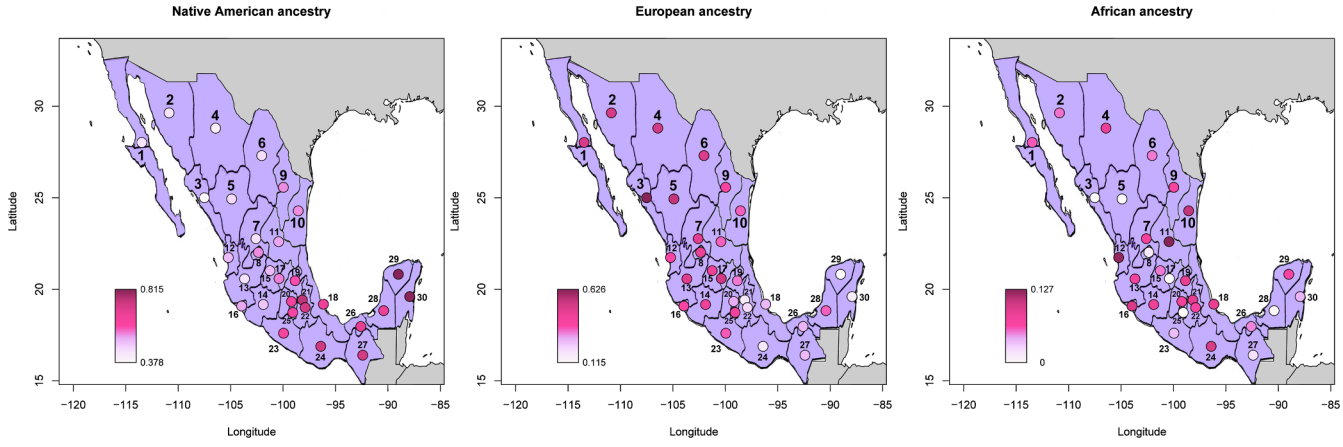

Fig. 1. Admixture proportions estimated from *HLA-A*, *-B* and *-DRB1* allelic frequencies for Mexico. Darker colors indicate an increasing proportion of that genetic component present in the studied population. Dots correspond to the geographic location of the capital city of each state, except for California (showing the geographic location of El Arco, in the limit between Baja California Norte and Baja California Sur) and Mexico City, which includes the State of Mexico. Each dot represents one analytical unit. 1: Baja California/Baja California Sur; 2: Sonora; 3: Sinaloa; 4: Chihuahua; 5: Durango; 6: Coahuila; 7: Zacatecas; 8: Aguascalientes; 9: Nuevo León; 10: Tamaulipas; 11: San Luis Potosí; 12: Nayarit; 13: Jalisco; 14: Michoacán; 15: Guanajuato; 16: Colima; 17: Querétaro; 18: Veracruz; 19: Hidalgo; 20: Mexico City/State of Mexico; 21: Tlaxcala; 22: Puebla; 23: Guerrero; 24: Oaxaca; 25: Morelos; 26: Tabasco; 27: Chiapas; 28: Campeche; 29: Yucatán; 30: Quintana Roo.

West, whereas PC2 (11.5% of the variance) separates Native Americans from non-Native Americans. In this PCA, the Mexican mixed-ancestry populations appear as a constellation spanning from a region populated by southeastern states and overlapping with Native American populations through an axis where northern and western states approach the European cluster (Fig. 2 and Supplementary Figs. 1 and 2), mimicking previous observations for Latin American mixed ancestry populations [45,93,101,102].

Both the heatmap of D_{ST} values for each pair of states (Fig. 3A and B) and the results of Barrier analysis (Fig. 3C) show that the Mexican states divide into three clearly discernible regions: both northwestern Mexico and southeastern Mexico appear as dense blocks in the heatmap due to their genetic relatedness probably due to the prevalent European or Maya Native American component, respectively (shown previously by other authors using genome-wide SNP data [13]), whereas a zone in central Mexico forms a more diffuse cluster (probably due to several distinct Native American components present there).

Fig. 4 shows the PIC and PD values (detailed in Supplementary Tables 8 and 9) for the 30 Mexican analytical units assessed, with values congruent with those from other mixed-ancestry Latin American populations [84,102]. Comparisons between observed and expected heterozygosity values for each analytical unit for estimating the HWE calculations can be found in Supplementary Fig. 4 and Supplementary Tables 10 and 11. Of the sample sets and analytical units analyzed, only five states were found to be in HWE for all four loci (Aguascalientes, Coahuila, Durango, Guanajuato and Guerrero). Five states showed no HWE for all four loci (Nuevo León, Tamaulipas, Mexico City, Puebla, and Campeche). *HLA-B* showed the most deviations from HWE (20 states), while *-DQB1* showed the least deviations (10 states) (Supplementary Tables 10 and 11).

4. Discussion

This study reports for the first time HLA class I and class II allele groups and haplotypes and HLA-based admixture proportions in populations from all the states of Mexico. Evidence of differential admixture reflected in haplotype frequencies and admixture estimates was found throughout Mexico, following a pattern from northwest to southeast mainly driven by the contribution of European (greater in the northwestern part of Mexico) and Native American (most represented in the south and southeastern parts of the country) ancestries. Interestingly, at the haplotypic level Mexican populations showed diverging genetic diversity. The fact that most states are differentiated from each other by the distribution of HLA haplotypes has implications for deceased donor organ allocation and HSC banking, in particular regarding the implementation of population-adjusted Panel Reactive Antibody (PRA) and the estimation of diversity required in a HSC bank [48].

Despite the large number of sample sets analyzed, the lack of two-field resolution data remains the major limitation of our study. Another important limitation is that most sample sets were found not to be in HWE. This could be due to ongoing selection events, but also due to massive migration events occurring throughout the country, thus affecting the demographic characteristics of Mexican mixed-ancestry populations for generations. In addition, although only unrelated individuals were included in the study, we cannot rule out an effect of sampling in these results. Due to the fact that data was collected between 2011 and 2016, several versions of the IPD-IMGT/HLA Database were used; to minimize this effect in the data reported, we checked all typings for ambiguities or changes in the nomenclature through time, with no major findings.

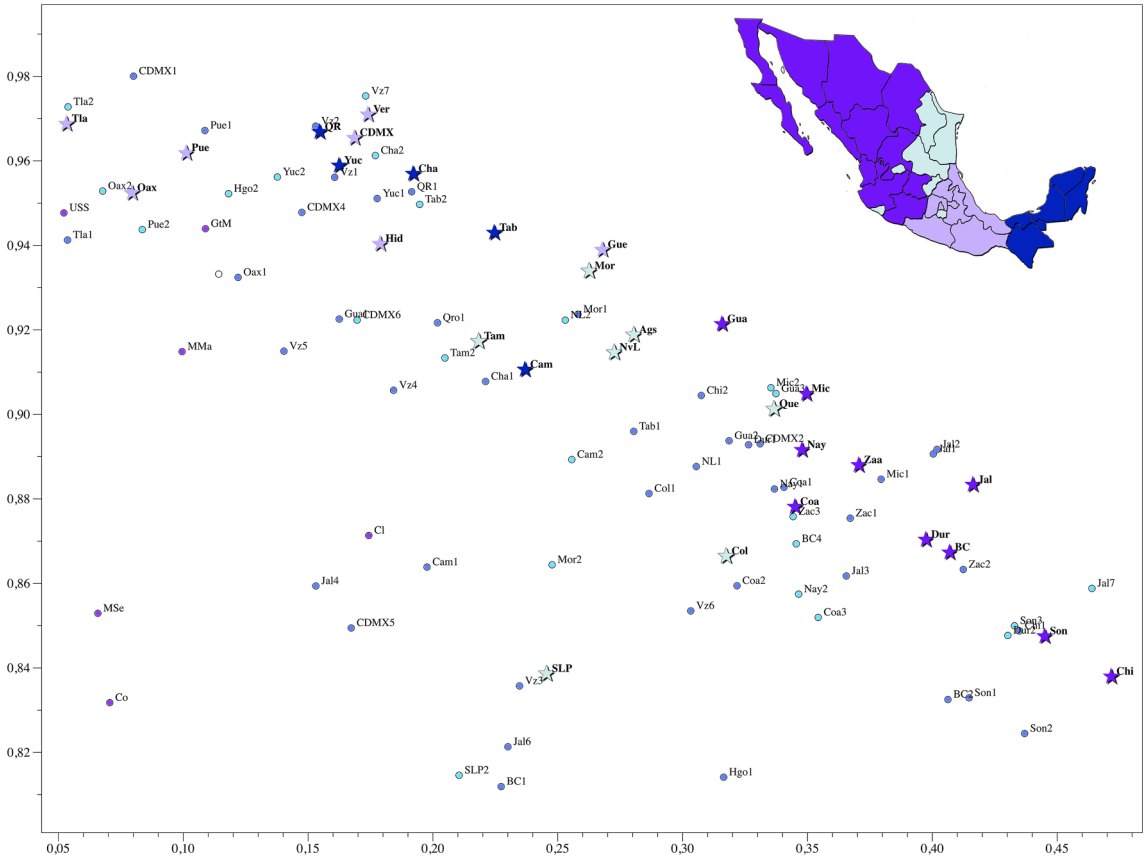

Fig. 2. Principal components analysis (PCA) using *HLA-B* and *-DRB1* frequencies. Please refer to Supplementary Fig. 3 for the complete PCA plot. For further information and references on the worldwide data sets, please refer to the Supplementary information section.

A

	BC	Son	Sin	Chi	Dur	Coa	Zac	Nay	Jal	Mic	Gua	Col	NL	Ags	Que	Tam	SLP	Ver	Hid	CDMX	Tla	Pue	Gue	Oax	Mor	Tab	Cha	Cam	Yuc	QRoo	
BC	0.0000	0.0008	0.0017	0.0012	0.0013	0.0008	0.0009	0.0007	0.0003	0.0002	0.0009	0.0053	0.0036	0.0042	0.0029	0.0018	0.0060	0.0063	0.0054	0.0062	0.0154	0.0113	0.0056	0.0152	0.0086	0.0098	0.0106	0.0094	0.0213	0.0158	BC
Son	0.0008	0.0000	0.0013	0.0020	0.0029	0.0020	0.0014	0.0032	0.0016	0.0010	0.0022	0.0070	0.0044	0.0037	0.0043	0.0040	0.0071	0.0077	0.0064	0.0078	0.0179	0.0134	0.0068	0.0173	0.0088	0.0119	0.0128	0.0129	0.0261	0.0196	Son
Sin	0.0017	0.0013	0.0000	0.0022	0.0022	0.0039	0.0036	0.0034	0.0025	0.0037	0.0036	0.0063	0.0084	0.0072	0.0047	0.0062	0.0117	0.0110	0.0109	0.0123	0.0243	0.0183	0.0085	0.0211	0.0105	0.0139	0.0159	0.0124	0.0281	0.0223	Sin
Chi	0.0012	0.0020	0.0022	0.0000	0.0023	0.0017	0.0010	0.0036	0.0008	0.0021	0.0025	0.0094	0.0040	0.0043	0.0055	0.0054	0.0075	0.0103	0.0079	0.0096	0.0199	0.0145	0.0076	0.0187	0.0104	0.0135	0.0152	0.0144	0.0279	0.0212	Chi
Dur	0.0013	0.0029	0.0022	0.0023	0.0000	0.0019	0.0020	0.0008	0.0015	0.0018	0.0011	0.0043	0.0049	0.0044	0.0029	0.0024	0.0079	0.0060	0.0070	0.0071	0.0158	0.0112	0.0046	0.0140	0.0059	0.0085	0.0097	0.0074	0.0196	0.0153	Dur
Coa	0.0008	0.0020	0.0039	0.0017	0.0019	0.0000	0.0002	0.0031	0.0010	0.0007	0.0004	0.0090	0.0018	0.0022	0.0049	0.0020	0.0035	0.0060	0.0031	0.0047	0.0122	0.0089	0.0056	0.0130	0.0072	0.0129	0.0132	0.0133	0.0255	0.0177	Coa
Zac	0.0009	0.0014	0.0036	0.0010	0.0020	0.0002	0.0000	0.0020	0.0001	0.0000	0.0004	0.0072	0.0020	0.0020	0.0052	0.0025	0.0031	0.0065	0.0041	0.0053	0.0140	0.0094	0.0056	0.0133	0.0076	0.0120	0.0123	0.0132	0.0245	0.0169	Zac
Nay	0.0007	0.0032	0.0034	0.0036	0.0008	0.0031	0.0020	0.0000	0.0011	0.0009	0.0012	0.0001	0.0053	0.0072	0.0025	0.0028	0.0062	0.0055	0.0076	0.0062	0.0151	0.0102	0.0044	0.0133	0.0070	0.0073	0.0073	0.0056	0.0153	0.0116	Nay
Jal	0.0003	0.0016	0.0025	0.0008	0.0015	0.0010	0.0001	0.0011	0.0000	0.0003	0.0007	0.0062	0.0032	0.0032	0.0043	0.0028	0.0044	0.0070	0.0057	0.0066	0.0155	0.0106	0.0056	0.0140	0.0082	0.0115	0.0121	0.0114	0.0228	0.0164	Jal
Mic	0.0002	0.0010	0.0037	0.0021	0.0018	0.0007	0.0000	0.0009	0.0003	0.0000	0.0000	0.0059	0.0024	0.0027	0.0026	0.0013	0.0031	0.0049	0.0036	0.0044	0.0128	0.0090	0.0046	0.0128	0.0061	0.0093	0.0093	0.0101	0.0204	0.0135	Mic
Gua	0.0009	0.0022	0.0036	0.0025	0.0011	0.0004	0.0004	0.0012	0.0007	0.0000	0.0000	0.0060	0.0022	0.0022	0.0020	0.0011	0.0037	0.0032	0.0024	0.0031	0.0108	0.0070	0.0029	0.0095	0.0042	0.0086	0.0088	0.0086	0.0185	0.0106	Gua
Col	0.0053	0.0070	0.0063	0.0094	0.0043	0.0090	0.0072	0.0001	0.0062	0.0059	0.0060	0.0000	0.0114	0.0109	0.0039	0.0080	0.0136	0.0075	0.0113	0.0096	0.0183	0.0140	0.0063	0.0151	0.0086	0.0073	0.0064	0.0047	0.0155	0.0136	Col
NL	0.0036	0.0044	0.0084	0.0040	0.0049	0.0018	0.0020	0.0053	0.0032	0.0024	0.0022	0.0114	0.0000	0.0012	0.0073	0.0024	0.0038	0.0047	0.0023	0.0028	0.0075	0.0043	0.0036	0.0088	0.0080	0.0125	0.0117	0.0152	0.0243	0.0166	NL
Ags	0.0042	0.0037	0.0072	0.0043	0.0044	0.0022	0.0020	0.0072	0.0032	0.0027	0.0022	0.0109	0.0012	0.0000	0.0059	0.0034	0.0048	0.0039	0.0004	0.0025	0.0079	0.0054	0.0029	0.0074	0.0039	0.0116	0.0110	0.0157	0.0260	0.0167	Ags
Que	0.0029	0.0043	0.0047	0.0055	0.0029	0.0049	0.0052	0.0025	0.0043	0.0026	0.0020	0.0039	0.0073	0.0059	0.0000	0.0054	0.0108	0.0041	0.0059	0.0057	0.0139	0.0114	0.0021	0.0127	0.0014	0.0029	0.0029	0.0057	0.0141	0.0086	Que
Tam	0.0018	0.0040	0.0062	0.0054	0.0024	0.0020	0.0025	0.0028	0.0028	0.0013	0.0011	0.0080	0.0024	0.0034	0.0054	0.0000	0.0063	0.0023	0.0023	0.0027	0.0080	0.0050	0.0028	0.0076	0.0077	0.0090	0.0095	0.0091	0.0191	0.0133	Tam
SLP	0.0060	0.0071	0.0117	0.0075	0.0079	0.0035	0.0031	0.0062	0.0044	0.0031	0.0037	0.0136	0.0038	0.0048	0.0108	0.0063	0.0000	0.0098	0.0052	0.0059	0.0126	0.0097	0.0105	0.0160	0.0092	0.0188	0.0173	0.0200	0.0300	0.0195	SLP
Ver	0.0063	0.0077	0.0110	0.0103	0.0060	0.0060	0.0065	0.0055	0.0070	0.0049	0.0032	0.0075	0.0047	0.0039	0.0041	0.0023	0.0098	0.0000	0.0017	0.0010	0.0041	0.0028	0.0001	0.0028	0.0039	0.0042	0.0038	0.0061	0.0116	0.0068	Ver
Hid	0.0054	0.0064	0.0109	0.0079	0.0070	0.0031	0.0041	0.0076	0.0057	0.0036	0.0024	0.0113	0.0023	0.0004	0.0059	0.0023	0.0052	0.0017	0.0000	-0.0002	0.0027	0.0024	0.0021	0.0049	0.0028	0.0093	0.0088	0.0120	0.0201	0.0118	Hid
CDMX	0.0062	0.0078	0.0123	0.0096	0.0071	0.0047	0.0053	0.0062	0.0066	0.0044	0.0031	0.0096	0.0028	0.0025	0.0057	0.0027	0.0059	0.0010	-0.0002	0.0000	0.0023	0.0018	0.0013	0.0039	0.0041	0.0073	0.0064	0.0101	0.0155	0.0093	CDMX
Tla	0.0154	0.0179	0.0243	0.0199	0.0158	0.0122	0.0140	0.0151	0.0155	0.0128	0.0108	0.0183	0.0075	0.0079	0.0139	0.0080	0.0126	0.0041	0.0027	0.0023	0.0000	0.0013	0.0050	0.0032	0.0097	0.0123	0.0100	0.0161	0.0187	0.0126	Tla
Pue	0.0113	0.0134	0.0183	0.0145	0.0112	0.0089	0.0094	0.0102	0.0106	0.0090	0.0070	0.0140	0.0043	0.0054	0.0114	0.0050	0.0097	0.0028	0.0024	0.0018	0.0013	0.0000	0.0027	0.0018	0.0087	0.0111	0.0092	0.0127	0.0170	0.0107	Pue
Gue	0.0056	0.0068	0.0085	0.0076	0.0046	0.0056	0.0056	0.0044	0.0056	0.0046	0.0029	0.0063	0.0036	0.0029	0.0021	0.0028	0.0105	0.0001	0.0021	0.0013	0.0050	0.0027	0.0000	0.0026	0.0031	0.0032	0.0027	0.0057	0.0127	0.0081	Gue
Oax	0.0152	0.0173	0.0211	0.0187	0.0140	0.0130	0.0133	0.0133	0.0140	0.0128	0.0095	0.0151	0.0088	0.0074	0.0127	0.0076	0.0160	0.0028	0.0049	0.0039	0.0032	0.0018	0.0026	0.0000	0.0103	0.0113	0.0095	0.0134	0.0165	0.0104	Oax
Mor	0.0086	0.0088	0.0105	0.0104	0.0059	0.0072	0.0076	0.0070	0.0082	0.0061	0.0042	0.0086	0.0080	0.0039	0.0014	0.0077	0.0092	0.0039	0.0028	0.0041	0.0097	0.0087	0.0031	0.0103	0.0000	0.0054	0.0058	0.0075	0.0146	0.0072	Mor
Tab	0.0098	0.0119	0.0139	0.0135	0.0085	0.0129	0.0120	0.0073	0.0115	0.0093	0.0086	0.0073	0.0125	0.0116	0.0029	0.0090	0.0188	0.0042	0.0093	0.0073	0.0123	0.0111	0.0032	0.0113	0.0054	0.0000	-0.0004	0.0012	0.0041	0.0040	Tab
Cha	0.0106	0.0128	0.0159	0.0152	0.0097	0.0132	0.0123	0.0073	0.0121	0.0093	0.0088	0.0064	0.0117	0.0110	0.0029	0.0095	0.0173	0.0038	0.0088	0.0064	0.0100	0.0092	0.0027	0.0095	0.0058	-0.0004	0.0000	0.0024	0.0048	0.0042	Cha
Cam	0.0094	0.0129	0.0124	0.0144	0.0074	0.0133	0.0132	0.0056	0.0114	0.0101	0.0086	0.0047	0.0152	0.0157	0.0057	0.0091	0.0200	0.0061	0.0120	0.0101	0.0161	0.0127	0.0057	0.0134	0.0075	0.0012	0.0024	0.0000	0.0029	0.0038	Cam
Yuc	0.0213	0.0261	0.0281	0.0279	0.0196	0.0255	0.0245	0.0153	0.0228	0.0204	0.0185	0.0155	0.0243	0.0260	0.0141	0.0191	0.0300	0.0116	0.0201	0.0155	0.0187	0.0170	0.0127	0.0165	0.0146	0.0041	0.0048	0.0029	0.0000	0.0011	Yuc
QRoo	0.0158	0.0196	0.0223	0.0212	0.0153	0.0177	0.0169	0.0116	0.0164	0.0135	0.0106	0.0136	0.0166	0.0167	0.0086	0.0133	0.0195	0.0068	0.0118	0.0093	0.0126	0.0107	0.0081	0.0104	0.0072	0.0040	0.0042	0.0038	0.0011	0.0000	QRoo
	BC	Son	Sin	Chi	Dur	Coa	Zac	Nay	Jal	Mic	Gua	Col	NL	Ags	Que	Tam	SLP	Ver	Hid	CDMX	Tla	Pue	Gue	Oax	Mor	Tab	Cha	Cam	Yuc	QRoo	

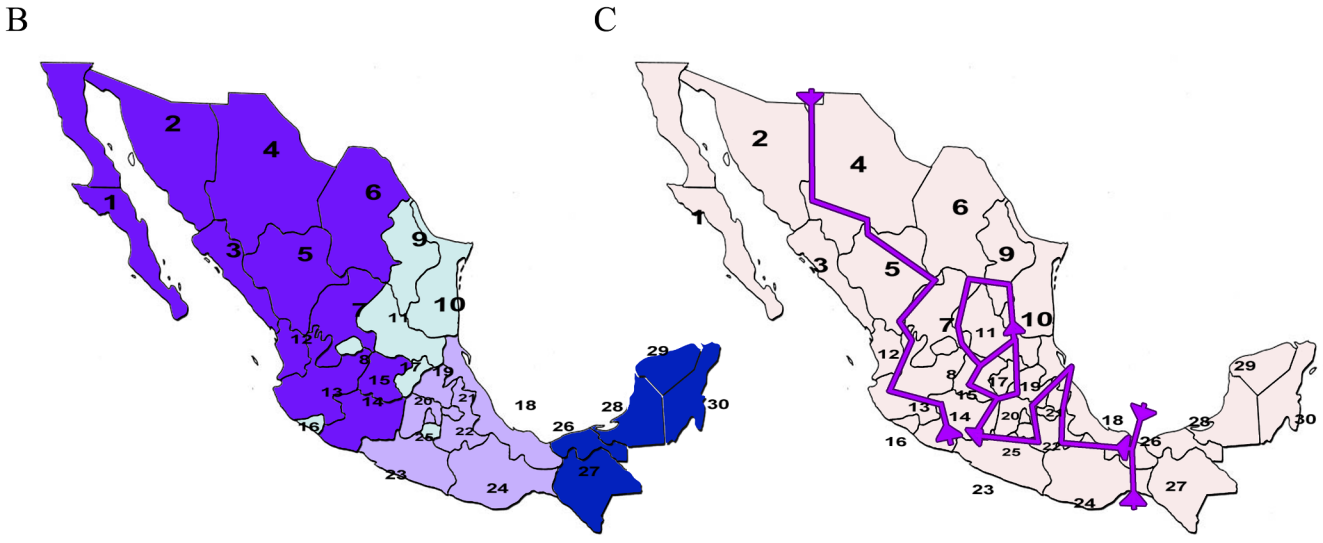

Fig. 3. Heatmap for the D_{ST} values for each pair of states of Mexico. A. The gradient from pale yellow to red indicates genetically close states, with strong red being the closest. The names of the states forming a well-defined cluster are shadowed in blue and purple. B. The states of Mexico colored as they cluster accordingly to D_{ST} values in Fig. 3A. C. *Barrier* analysis showing major genetic barriers within Mexico. Purple lines indicate the genetic barriers found. Each dot represents one analytical unit. 1: Baja California/Baja California Sur (BC); 2: Sonora (Son); 3: Sinaloa (Sin); 4: Chihuahua (Chi); 5: Durango (Dur); 6: Coahuila (Coa); 7: Zacatecas (Zac); 8: Aguascalientes (Ags); 9: Nuevo León (NL); 10: Tamaulipas (Tam); 11: San Luis Potosí (SLP); 12: Nayarit (Nay); 13: Jalisco (Jal); 14: Michoacán (Mic); 15: Guanajuato (Gua); 16: Colima (Col); 17: Querétaro (Que); 18: Veracruz (Ver); 19: Hidalgo (Hid); 20: Mexico City/State of Mexico (CDMX); 21: Tlaxcala (Tla); 22: Puebla (Pue); 23: Guerrero (Gue); 24: Oaxaca (Oax); 25: Morelos (Mor); 26: Tabasco (Tab); 27: Chiapas (Cha); 28: Campeche (Cam); 29: Yucatán (Yuc); 30: Quintana Roo (QRoo).

4.1. Admixture estimates in Mexican populations and immunogenetic diversity

HLA-based admixture estimates follow roughly the same patterns observed in genome-wide estimation studies [1,2,159] with an increase in Native American ancestry towards south and south-eastern Mexico and an increase in European genetic contribution in the exact opposite direction. The increase of Native American ancestry from northwestern to southeastern Mexico mimics the distribution of indigenous languages native speakers [160]. African ancestry does not follow a specific discernible pattern, although it is more prevalent in the central and southern part of the country, which is consistent with historical records [19,21]. Higher levels of diversity (by means of PIC and PD) occur in the northern part of the country, coinciding with higher estimations of European contribution (Fig. 4) and previous reports based on heterozygosity values obtained from genome-wide SNP data [159] and consistent with previous reports for other mixed ancestry populations from Latin America [102].

Interestingly, no clear pattern arose from the HWE and heterozygosity calculations, although Mexico City was previously reported not to be in HWE for *HLA-B* and *HLA-DRB1* genes and showing a slightly lower than expected observed heterozygosity [154]. Nuevo León also had significant deviations from the HWE but in this case it is due to those sample sets exhibiting a higher than expected heterozygosity for *HLA-B* and *-DQB1* (Supplementary Table 10). This is in line with previous findings for *HLA-B* [154] and could be due to intense migration of individuals coming from states with different proportions of ancestral genetic components, specifically a higher proportion of Native American ancestry [154,161]. The fact that mixed ancestry populations from southeastern Mexico also exhibit some lower than expected heterozygosity values (Supplementary Table 10 and Supplementary Fig. 4) further supports Native American ancestry affecting HWE [41,162].

4.2. The Native American immunogenetic component in Mexican populations

Around 80% of the most frequent haplotypes and the vast majority

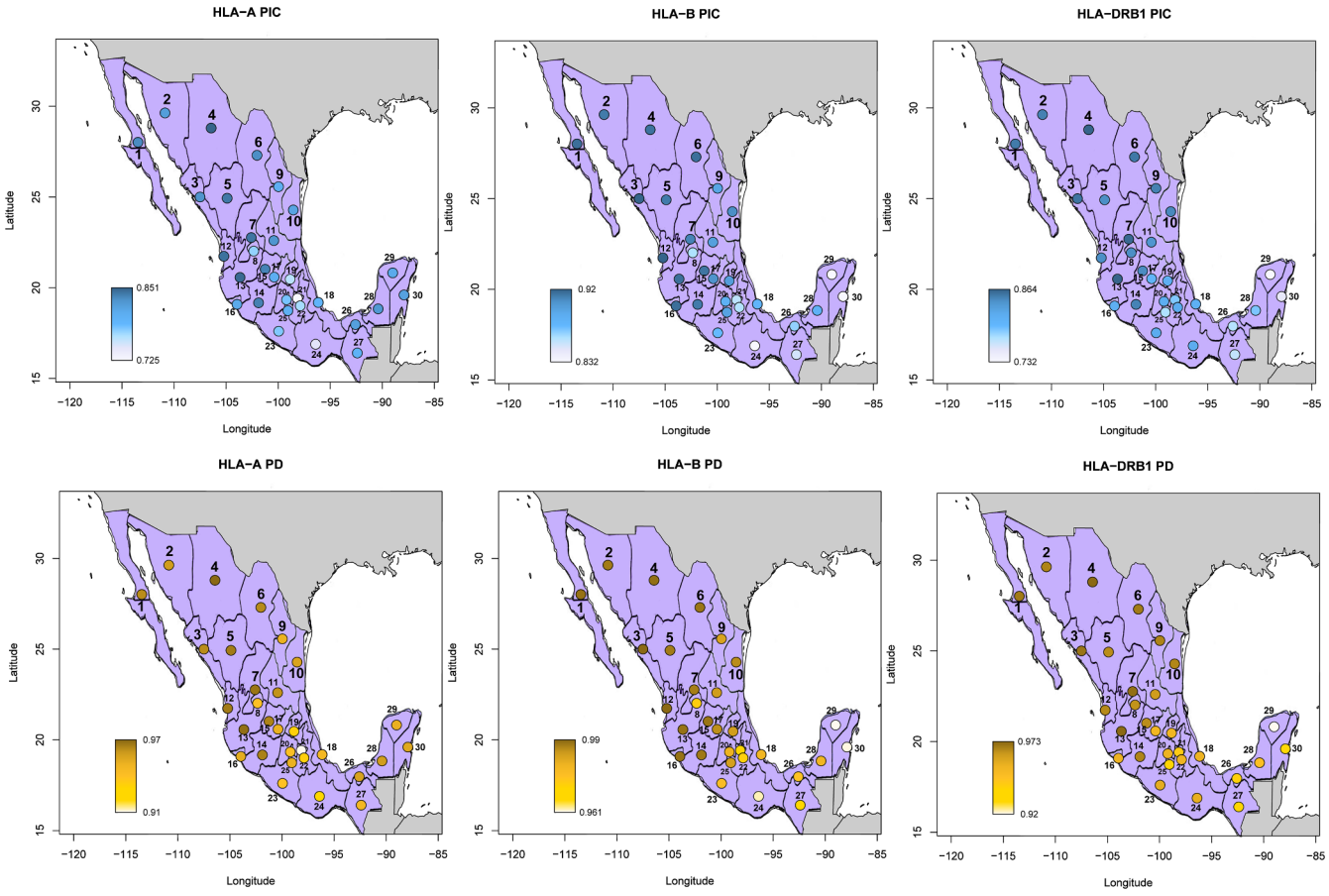

Fig. 4. Polymorphism informative content (PIC, in blue) and power of discrimination (PD, in gold) calculated for *HLA-A*, *-B* and *-DRB1* allelic frequencies in Mexico. Darker colors indicate an increasing value of the parameter in the studied population. Dots correspond to the geographic location of the capital city of each state, except for California (showing the geographic location of El Arco, in the limit between Baja California Norte and Baja California Sur) and Mexico City, which includes the State of Mexico. Each dot represents one analytical unit. 1: Baja California/Baja California Sur; 2: Sonora; 3: Sinaloa; 4: Chihuahua; 5: Durango; 6: Coahuila; 7: Zacatecas; 8: Aguascalientes; 9: Nuevo León; 10: Tamaulipas; 11: San Luis Potosí; 12: Nayarit; 13: Jalisco; 14: Michoacán; 15: Guanajuato; 16: Colima; 17: Querétaro; 18: Veracruz; 19: Hidalgo; 20: Mexico City/State of Mexico; 21: Tlaxcala; 22: Puebla; 23: Guerrero; 24: Oaxaca; 25: Morelos; 26: Tabasco; 27: Chiapas; 28: Campeche; 29: Yucatán; 30: Quintana Roo.

of HLA allele group diversity in Mexican populations are of Native American origin, which pinpoints the importance of such a component across Mexican mixed-ancestry populations. For example, HLA-DRB1*04 is a signature marker for Native American ancestry in Mexican mixed-ancestry populations, with seven out of the nine HLA haplotypes with frequencies above 1% in the country carrying DRB1*04. Not only is it evenly distributed throughout the country, but its frequencies within Mexico are among the highest at a worldwide level [36]. Neighboring Native American and mixed-ancestry populations bearing the allele at high frequencies support this MPA. This is the case for southeastern Mexico and Maya populations, in which DRB1*04 reaches frequencies of 0.4635 for Yucatán state (estimated Native American genetic contribution of 81.5%) and 0.7330 in Mexican [116] and 0.4910 in Guatemalan [129] Maya populations. Genetic variants from one of the parental populations that are advantageous to individuals in the admixed population can rise in frequency and thus cause an over-representation of a specific parental ancestry in the genomic region under selection [163]. Interestingly, the HLA class II genomic region has been previously reported to have undergone selective pressure after the conquest [164], which could be linked to the pattern found for this class II allele in modern Mexicans.

4.3. Implications of the study of alleles and haplotypes of the HLA system in Mexican populations and final considerations

Allele groups, allelic and haplotypic frequencies of the HLA genes are important in the context of autoimmune conditions, clinical decisions in transplantation of both solid organs and hematopoietic precursors, and pharmacogenetics. In this work, we present data on the distribution of clinically relevant variants in Mexican populations that may be of interest for researchers and professionals in these areas. In recent years, some HLA alleles (HLA-B*15:02, B*57:01, and B*58) have been associated with important clinical phenotypes (abacavir sensitivity, flucloxacillin-induced hepatitis, HIV progression resistance, allopurinol-induced hypersensitivity, epidermal necrosis and Stevens-Johnson syndrome, etc.) [31,165–177]. In some of these cases, genetic testing has been recommended by the health authorities of the country [174,175]. Knowledge of the extent of differential admixture may shed light onto the underlying reasons for the observed prevalence of these alleles and the differential risk in each Mexican population.

Data on HLA allele group frequencies is also relevant for PRA and Single Antigen (LSA) testing to adjust PRA percentage values and to report specificities that could be relevant to Mexican populations, ultimately leading to the development of “virtual crossmatching” (i.e. population-adjusted PRA). Also, allelic and haplotypic information may be of interest for deceased kidney donor allocation programs and in the development of stem cell repositories such as cord blood banking

[34,132] and in marrow donor programs, as they are useful for estimating the probability of finding a match in a particular population and adjusting priority on waiting lists [29,178].

5. Conclusion

Here we provided important elements to demonstrate the underlying structure of the HLA genetic system diversity in Mexican populations for the whole country. Even though we have a large sample size, we must not omit that our conclusions are based on low-intermediate resolution data, and a finer analysis could be obtained with a responsible interpretation of high-resolution data [39,179], which would allow researchers to draw more precise demographic or selection signatures, as well as a better understanding of the allelic diversity within Mexican mixed-ancestry populations. Nevertheless, our data will help to better understand the differential distribution of allele groups and haplotypes across Mexican mixed-ancestry populations, the underlying genetic structure in modern Mexican populations, and its implication in donor-recipient matching, pharmacogenetics, and epidemic events.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2020.06.008.

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