Human Immunology 81 (2020) 461–474

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

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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https://doi.org/10.1016/j.humimm.2020.06.008

Available online 08 July 2020

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ARTICLE INFO

Keywords:
HLA
Immunogenetics
Population genetics
Genetic substructure
Admixture
Latin American populations
Mexico

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 [102] 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

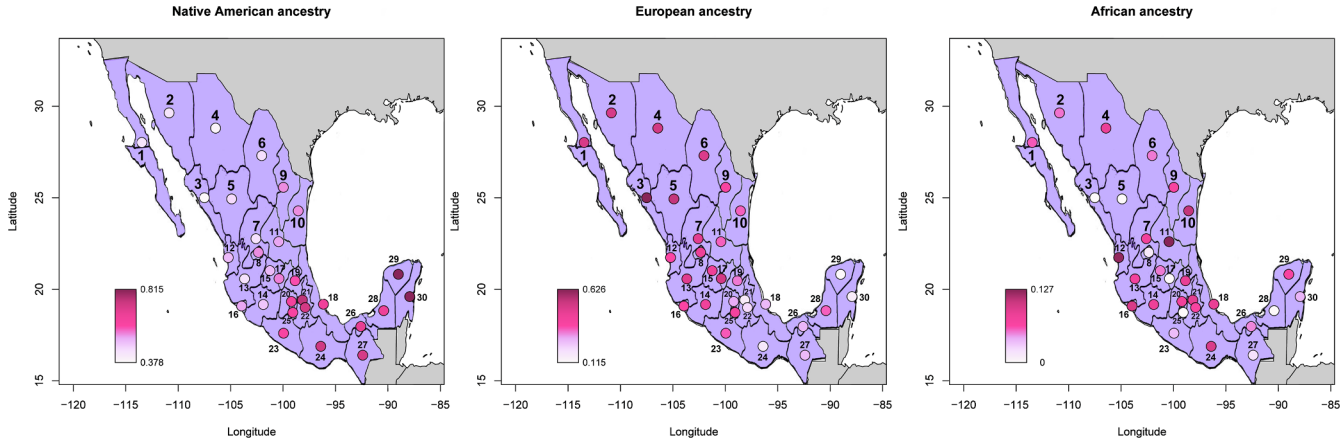

Fig. 1. Admixture proportions estimated from *HLA-A, -B* and *-DRB1* allelic frequencies for Mexico. Darker colors indicate an increasing proportion of that genetic component present in the studied population. Dots correspond to the geographic location of the capital city of each state, except for California (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.

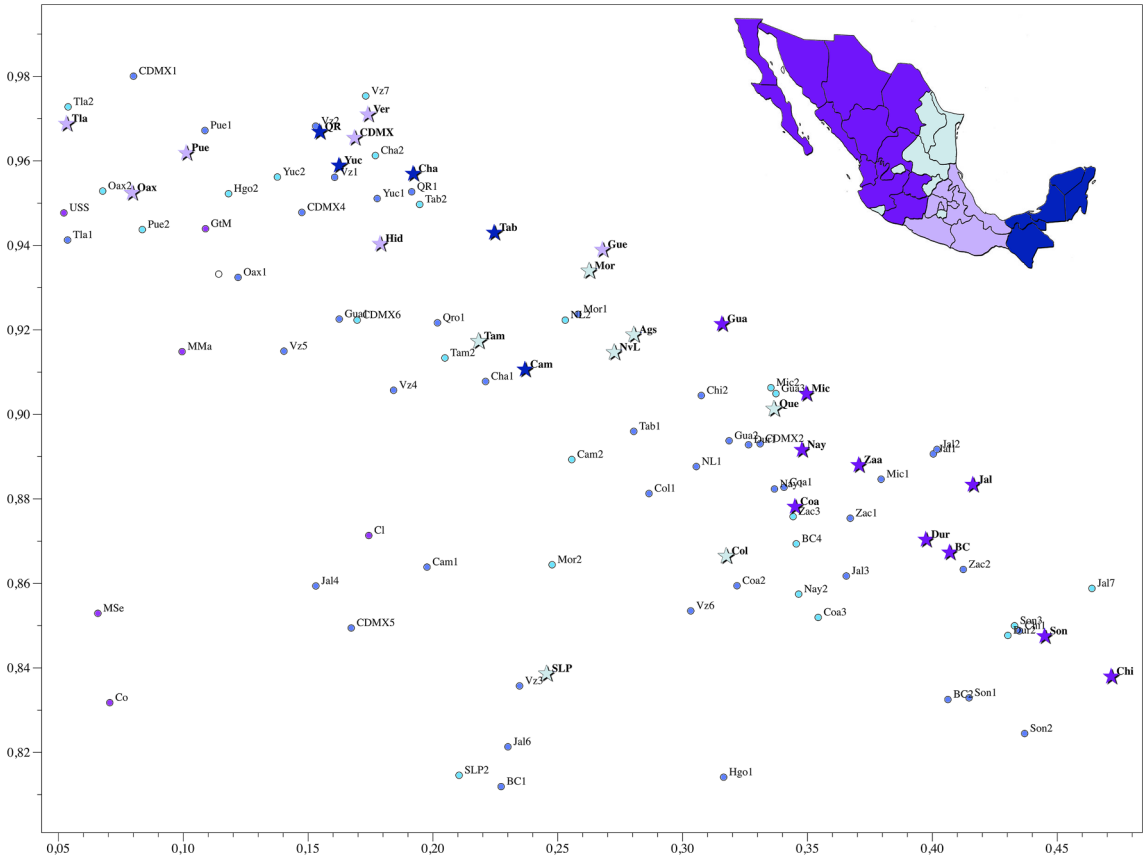

Fig. 2. Principal components analysis (PCA) using *HLA-B* and *-DRB1* frequencies. Please refer to Supplementary Fig. 3 for the complete PCA plot. For further information and references on the worldwide data sets, please refer to the Supplementary information section.

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	

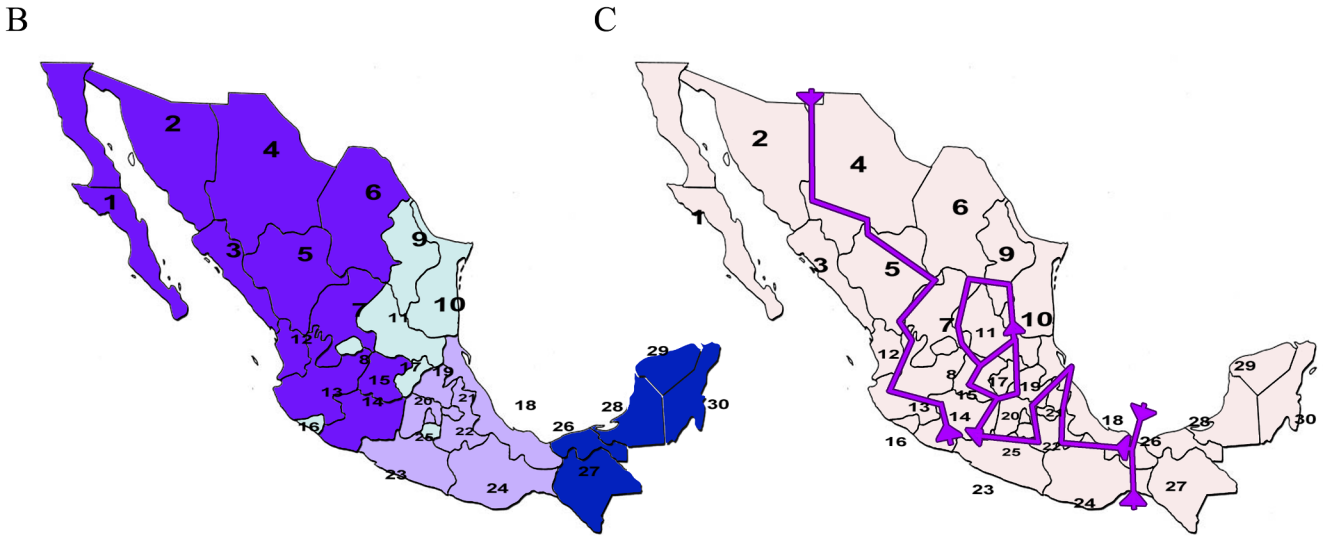

Fig. 3. Heatmap for the D_{ST} values for each pair of states of Mexico. A. The gradient from pale yellow to red indicates genetically close states, with strong red being the closest. The names of the states forming a well-defined cluster are shadowed in blue and purple. B. The states of Mexico colored 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

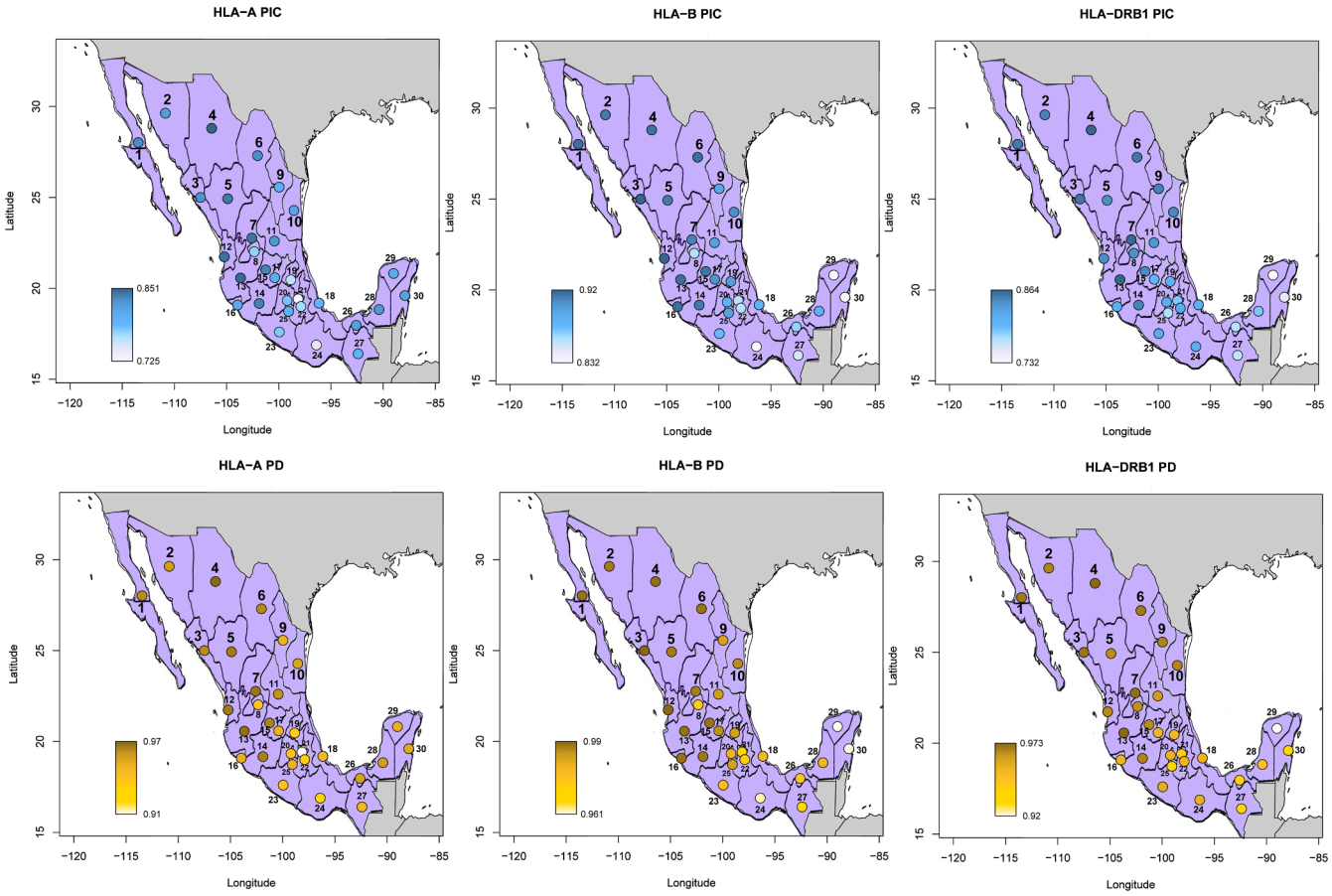

Fig. 4. Polymorphism informative content (PIC, in blue) and power of discrimination (PD, in gold) calculated for *HLA-A*, *-B* and *-DRB1* allelic frequencies in Mexico. Darker colors indicate an increasing value of the parameter in the studied population. Dots correspond to the geographic location of 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.

Acknowledgements

The authors would like to pay tribute to Prof. Francisco Mauro Salzano (1928-2018), who recently passed away, for him inspired a whole generation of Latin American anthropologists, human biologists and geneticists to explore the complexity of Latin American populations. His legacy prevails in several academic texts inspired by his work and view, such as the present manuscript. The authors acknowledge the valuable support of Técnicas Genéticas Aplicadas a la Clínica, S.A. de C.V., Amplibio, S.A. de C.V. and Laboratorios Diagnomol, S.A. de C.V. in various stages of development of the present work. We are particularly grateful to the anonymous reviewers and to Derek Middleton, whom with their committed effort enriched our paper. The authors thank Stephan Schiffels for his support in the admixture proportions analysis and helpful discussions. We are grateful to Raquel Fabiola Hernández Díaz, Victoria Paola García Pérez, María Lourdes Gasca Leyva and Adrián García Soto for their important support. The authors want to express their gratitude to Magdalena Limones, Oscar Jaramillo Muñoz, Jaime Guadalupe Valle Leal, Marcela Liliana Flores Martínez, Margarita Valdez González, Erika Elizabeth González Zapata, Rubén Jardón Pérez, Ileana Raquel Hernández Araiza, Anaí Balbuena Jaime, Iván Pedroza Reyes, Arturo Pacho Varela, Víctor Aramburu Cano, Mónica Ballesteros Romero, Paola Everardo Martínez, Francisco de Ávila Becerril, Miguel Ángel Contreras Sieck, Martha Granados Riveros, Ilich Jafet Moreno, Diana Rogel Díaz, Paola León Mimila, Fabiola González Martínez, Venecia Wendoline Mejia Arredondo, Sandra Cristina González Garfio, Fernando Aguirre Mendoza, Antonio González Martín, Michael Crawford, Christina Warinner, Oana del Castillo Chávez, Alondra Victoria Trejo Ordoz, Laura Curiel Giles, Juan Manuel Argüelles San Millán, Thiseas Lamnidis, Eirini Skourtanioti, Cosimo Posth and Maria Spyrou for their committed technical, logistical and analytical support, including volunteer recruitment, sample processing and data entry and edition as well as insightful discussions in various stages of the present study. The authors wish to thank all participants who benefited our study with their time and sample(s). This project was possible with the joint support from multiple institutions in Mexico. This project was partly funded and supported by the Max Planck Society, the National Committee of Scientific Research and the Health Research Fund (FIS) from the Instituto Mexicano del Seguro Social (IMSS) (Registries: 2013-3501-1, FIS/IMSS/PROT/G11/952 and R-2015-785-078) and grants from the Leverhulme Trust (F/07 134/DF to A.R.-L.), BBSRC (BB/I021213/1 to A.R.-L.), Universidad de Antioquia (CODI sostenibilidad de grupos 2013-2014 and MASO 2013-2014), Conselho Nacional de Desenvolvimento Científico e Tecnológico, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (Apoio a Núcleos de Excelência Program) and Fundação de Aperfeiçoamento de Pessoal de Nível Superior. All data from our sample sets, both frequencies and individual genotypes, can be found at The Allele Frequency Net Database website (www.allelefrequencies.net).

Appendix A. Supplementary data

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

References

[1] A. Ruiz-Linares, K. Adhikari, V. Acuña-Alonzo, M. Quinto-Sanchez, C. Jaramillo, W. Arias, et al., Admixture in Latin America: geographic structure, phenotypic diversity and self-perception of ancestry based on 7,342 individuals, PLoS Genet. 10 (2014) e1004572, , https://doi.org/10.1371/journal.pgen.1004572.
[2] J.M. Kidd, S. Gravel, J. Byrnes, A. Moreno-Estrada, S. Musharoff, K. Bryc, et al., Population genetic inference from personal genome data: Impact of ancestry and admixture on human genomic variation, Am. J. Hum. Genet. 91 (2012) 660–671.
[3] J.S. Marr, J.B. Kiracofe, Was the huey cocoliztli a haemorrhagic fever? Med. Hist. 44 (2000) 341–362, https://doi.org/10.1017/S0025727300066746.
[4] S.M. Deeds, Legacies of resistance, adaptation, and tenacity: history of the Native Peoples of Northwest Mexico, in: R.E.W. Adams, M.J. Macleod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. II. Mesoamerica. Part 2, Cambridge University Press, Cambridge, 2008: pp. 44–88.
[5] S. Deans Smith, Native Peoples of the Gulf Coast from the Colonial Period to the Present, in: R.E.W. Adams, M.J. MacLeod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. II, Mesoamerica, Cambridge University Press, Cambridge, 2008: pp. 274–301.
[6] D. Frye, The Lowland Maya, from the Conquest to the Present, in: R.E.W. Adams, M.J. MacLeod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. II, Mesoamerica, Cambridge University Press, Cambridge, 2008: pp. 89–135.
[7] E. van Young, The Indigenous Peoples of Western Mexico from the Spanish Invasion to the Present, in: R.E.W. Adams, M.J. MacLeod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. I, Mesoamerica, Cambridge University Press, Cambridge, 2008: pp. 136–186.
[8] S.L. Cline, Native Peoples of Colonial Central Mexico, in: R.E.W. Adams, M.J. MacLeod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. II, Mesoamerica, Cambridge University Press, Cambridge, 2008: pp. 187–222.
[9] G.D. Jones, The Native Peoples of Northeastern Mexico, in: R.E.W. Adams, M.J. MacLeod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. II, Mesoamerica. Part 2, Cambridge University Press, Cambridge, 2008: pp. 346–391.
[10] M. de los Á. Romero Frizzi, The Indigenous of Oaxaca from the Sixteenth Century to the Present, in: R.E.W. Adams, M.J. MacLeod (Eds.), Cambridge Hist. Nativ. Peoples Am. Vol. II, Mesoamerica, Cambridge University Press, Cambridge, 2008: pp. 302–345.
[11] F.M. Salzano, Molecular variability in Amerindians: widespread but uneven information, An. Acad. Bras. Cienc. 74 (2002) 223–263, https://doi.org/10.1590/S0001-37652002000200005.
[12] A. Gorostiza, V. Acunha-Alonzo, L. Regalado-Liu, S. Tirado, J. Granados, D. Sámano, et al., Reconstructing the history of mesoamerican populations through the study of the mitochondrial DNA control region, PLoS ONE 7 (2012), https://doi.org/10.1371/journal.pone.0044666.
[13] A. Moreno-Estrada, C.R. Gignoux, J.C. Fernández-López, F. Zakharia, M. Sikora, A.V. Contreras, et al., The genetics of Mexico recapitulates Native American substructure and affects biomedical traits, Science 344 (2014) 1280–1285, https://doi.org/10.1126/science.1251688.
[14] A. González-Martín, A. Gorostiza, L. Regalado-Liu, S. Arroyo-Peña, S. Tirado, I. Nuño-Arana, et al., Demographic history of indigenous populations in Mesoamerica based on mtDNA sequence data, PLoS ONE 10 (2015), https://doi.org/10.1371/journal.pone.0131791.
[15] D. Reich, N. Patterson, D. Campbell, A. Tandon, S. Mazieres, N. Ray, et al., Reconstructing Native American population history, Nature 488 (2012) 370–374, https://doi.org/10.1038/nature11258.
[16] S. Romero-Hidalgo, A. Ochoa-Leyva, A. Garcíarrubio, V. Acuña-Alonzo, E. Antúnez-Argüelles, M. Balcazar-Quintero, et al., Demographic history and biologically relevant genetic variation of Native Mexicans inferred from whole-genome sequencing, Nat. Commun. 8 (2017), https://doi.org/10.1038/s41467-017-01194-z.
[17] J. Buchenau, Small numbers, great impact: Mexico and its immigrants, 1821–1973, J. Am. Ethn. Hist. 20 (2001) 23–49, https://doi.org/10.2307/27502710.
[18] B. Grunberg, El universo de los conquistadores: resultado de una investigación prosopográfica, Signos Históricos. 12 (2004) 94–118.

[19] G. Aguirre Beltrán, The Slave Trade in Mexico, Hisp. Am. Hist. Rev. 24 (1944) 412–431.
[20] R. Lisker, A. Loria, M.S. Cordova, Studies on several genetic hematological traits of the Mexican population. 8. Hemoglobin s, glucose-6-phosphate dehydrogenase deficiency, and other characteristics in a malarial region, Am. J. Hum. Genet. 17 (1965) 179–187.
[21] G. Aguirre Beltrán, La población negra en México: Estudio etnohistórico, 2nd. Ed., Fondo de Cultura Económica (FCE), Mexico City, 1972.
[22] P.E. Lovejoy, The volume of the Atlantic Slave Trade: a synthesis, J. Afr. Hist. 23 (1982) 473–501 https://www.jstor.org/stable/182037.
[23] P.E. Lovejoy, Esclavitud y comercio esclavista en el África Occidental: investigaciones en curso, in: M.E. Velázquez (Ed.), Debates Históricos Contemp. Africanos y Afrodescendientes En México y Centroamérica, Centro de Estudios Mexicanos y Centroamericanos, Mexico City, 2011: pp. 35–57. doi:10.4000/books.cemca.182.
[24] J. Axtell, The columbian mosaic in colonial America, Humanities 12 (1991) 12–18.
[25] E. Hu-Dehart, The Chinese of Peru, Cuba, and Mexico, in: R. Cohen (Ed.), Cambridge Surv. World Migr., Cambridge University Press, Cambridge, 1995: pp. 220–391.
[26] S. Xu, Los chinos a lo largo de la historia de México, in: E. Dussel Peters, Y. Trápaga Delfín (Eds.), China y México Implicaciones Una Nueva Relación, 1st Ed, Universidad Nacional Autónoma de México (UNAM), Fundación Friedrich Ebert, Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM), La Jornada Ediciones/Demos, Mexico City, 2007: pp. 51–68.
[27] INEGI, Los extranjeros en México, Mexico City, 2014. Doi:10.1016/0306-4522(87)92980-0.
[28] A.M. Pardo Montaño, C.A. Dávila Cervantes, Extranjeros residentes en México. Perfil sociodemográfico, ocupación y distribución geográfica en 2015, Cart. Económica Reg. CER. 28 (2016) 31–51.
[29] J.M. Tiercy, F. Claas, Impact of HLA diversity on donor selection in organ and stem cell transplantation, Hum. Hered. 76 (2014) 178–186, https://doi.org/10.1159/000358798.
[30] J.H. Karnes, L. Bastarache, C.M. Shaffer, S. Gaudieri, Y. Xu, A.M. Glazer, et al., Phenome-wide scanning identifies multiple diseases and disease severity phenotypes associated with HLA variants, Sci. Transl. Med. 9 (2017) 1–13, https://doi.org/10.1126/scitranslmed.aai8708.
[31] R. Pavlos, S. Mallal, E. Phillips, HLA and pharmacogenetics of drug hypersensitivity, Pharmacogenomics 13 (2012) 1285–1306, https://doi.org/10.2217/pgs.12.108.
[32] T. Profaizer, HLA Alleles and Drug Hypersensitivity Reactions, ASHI Q. (2010).
[33] C. Neumann-Haefelin, C. Oniangue-Ndza, T. Kuntzen, J. Schmidt, K. Nitschke, J. Sidney, et al., Human leukocyte antigen B27 selects for rare escape mutations that significantly impair hepatitis C virus replication and require compensatory mutations, Hepatology 54 (2011) 1157–1166, https://doi.org/10.1002/hep.24541.
[34] M. Yawata, N. Yawata, M. Draghi, A.-M. Little, F. Partheniou, P. Parham, Roles for HLA and KIR polymorphisms in natural killer cell repertoire selection and modulation of effector function, J. Exp. Med. 203 (2006) 633–645, https://doi.org/10.1084/jem.20051884.
[35] V. Müller, L. Kemény, B. Papp, G. Boross, M. Manczinger, T.L. Lenz, et al., Pathogen diversity drives the evolution of generalist MHC-II alleles in human populations, PLOS Biol. (2019) 1–21, https://doi.org/10.1371/journal.pbio.3000131.
[36] E.J.M. dos Santos, A. McCabe, F.F. Gonzalez-Galarza, A.R. Jones, D. Middleton, Allele Frequencies Net Database: Improvements for storage of individual genotypes and analysis of existing data, Hum. Immunol. 77 (2016) 238–248, https://doi.org/10.1016/j.humimm.2015.11.013.
[37] S. Buhler, A. Sanchez-Mazas, HLA DNA sequence variation among human populations: Molecular signatures of demographic and selective events, PLoS ONE 6 (2011), https://doi.org/10.1371/journal.pone.0014643.
[38] A. Sanchez-Mazas, S. Buhler, J.M. Nunes, A new HLA map of Europe: Regional genetic variation and its implication for peopling history, disease-association studies and tissue transplantation, Hum. Hered. 76 (2014) 162–177, https://doi.org/10.1159/000360855.
[39] A. Sanchez-Mazas, J.M. Nunes, Does NGS typing highlight our understanding of HLA population diversity?: Some good reasons to say yes and a few to say be careful, Hum. Immunol. (2018) 1–5, https://doi.org/10.1016/j.humimm.2018.10.004.
[40] K. Cao, A.M. Moormann, K.E. Lyke, C. Masaberg, O.P. Sumba, O.K. Doumbo, et al., Differentiation between African populations is evidenced by the diversity of alleles and haplotypes of HLA class I loci, Tissue Antigens 63 (2004) 293–325, https://doi.org/10.1111/j.0001-2815.2004.00192.x.
[41] J.A. Hollenbach, G. Thomson, K. Cao, M. Fernandez-Vina, H.A. Erlich, T.L. Bugawan, et al., HLA diversity, differentiation, and haplotype evolution in mesoamerican natives, Hum. Immunol. 62 (2001) 378–390, https://doi.org/10.1016/S0198-8859(01)00212-9.
[42] K. Cao, J. Hollenbach, X. Shi, W. Shi, M. Chopek, M.A. Fernández-Viña, Analysis of the frequencies of HLA-A, B, and C alleles and haplotypes in the five major ethnic groups of the United States reveals high levels of diversity in these loci and contrasting distribution patterns in these populations, Hum. Immunol. 62 (2001) 1009–1030, https://doi.org/10.1016/S0198-8859(01)00298-1.
[43] M. Maiers, L. Gragert, W. Klitz, High-resolution HLA alleles and haplotypes in the United States population, Hum. Immunol. 68 (2007) 779–788, https://doi.org/10.1016/j.humimm.2007.04.005.
[44] P.A. Gourraud, P. Khankhanian, N. Cereb, S.Y. Yang, M. Feolo, M. Maiers, et al., HLA diversity in the 1000 genomes dataset, PLoS ONE 9 (2014), https://doi.org/10.1371/journal.pone.0097282.
[45] E. Arrieta-Bolaños, J.A. Madrigal, B.E. Shaw, Human leukocyte antigen profiles of Latin American populations: differential admixture and its potential impact on hematopoietic stem cell transplantation, Bone Marrow Res. 2012 (2012) 1–13, https://doi.org/10.1155/2012/136087.
[46] A. Bravo-Acevedo, R. Barquera, C. Bekker-Méndez, S. Clayton, D.I. Hernández-Zaragoza, G. Benítez-Arvizu, et al., HLA concordance between hematopoietic stem cell transplantation patients and umbilical cord blood units: Implications for cord blood banking in admixed populations, Hum. Immunol. 80 (2019) 714–722, https://doi.org/10.1016/j.humimm.2019.05.002.
[47] E. Arrieta-Bolaños, D.C. Oliveira, R. Barquera, Differential admixture, human leukocyte antigen diversity, and hematopoietic cell transplantation in Latin America: challenges and opportunities, Bone Marrow Transplant. (2019), https://doi.org/10.1038/s41409-019-0737-4.
[48] K. Haimila, A. Penttilä, A. Arvola, M.K. Auvinen, M. Korhonen, Analysis of the adequate size of a cord blood bank and comparison of HLA haplotype distributions between four populations, Hum. Immunol. 74 (2013) 189–195, https://doi.org/10.1016/j.humimm.2012.10.018.
[49] J. Dehn, S. Spellman, C.K. Hurley, B.E. Shaw, J.N. Barker, L.J. Burns, et al., Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR, Blood 134 (2019) 924–934, https://doi.org/10.1182/blood.2019001212.
[50] R. Barquera-Lozano, El papel de la genética de poblaciones en la inmunología del trasplante en México, Gac. Med. Mex. 148 (2012) 52–67.
[51] S.J. Mack, D. Middleton, Introducing a new manuscript format: enabling access to immunogenomic population data with short population reports, Hum. Immunol. 76 (2015) 393–394, https://doi.org/10.1016/j.humimm.2015.03.014.
[52] A. Escobedo-Ruíz, R. Barquera, A. González-Martín, J.M. Argüelles-San Millán, M.G. Uribe-Duarte, D.I. Hernández-Zaragoza, et al., Genetic diversity of HLA system in four populations from Baja California, Mexico: Mexicali, La Paz, Tijuana and rural Baja California, Hum. Immunol. 81 (2020) 475–477, https://doi.org/10.1016/j.humimm.2019.06.007.
[53] M.G. Uribe-Duarte, J.A. Aguilar-Campos, R. Barquera, A. Bravo-Acevedo, S. Clayton, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in three populations from Sonora, Mexico: Ciudad Obregón, Hermosillo and rural Sonora, Hum. Immunol. 81 (2020) 478–481, https://doi.org/10.1016/j.humimm.2019.05.013.
[54] J.A. Pantoja-Torres, R. Barquera, M. Ballesteros-Romero, A. Bravo-Acevedo, E. Arrieta-Bolaños, G.D. Montiel-Hernández, et al., Genetic diversity of HLA system in three populations from Guanajuato, Mexico: Guanajuato City, León and rural Guanajuato, Hum. Immunol. 81 (2020) 510–512, https://doi.org/10.1016/j.humimm.2019.06.002.
[55] R. Barquera, D.I. Hernández-Zaragoza, F.P. Arellano-Prado, I. Goné-Vázquez, S. Clayton, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Colima, Mexico: Colima city and rural Colima, Hum. Immunol. 81 (2020) 513–515, https://doi.org/10.1016/j.humimm.2019.06.004.
[56] R. Barquera, A. Bravo-Acevedo, S. Clayton, T.J.R. Munguía, D.I. Hernández-Zaragoza, C. Adalid-Sáinz, et al., Genetic diversity of HLA system in two populations from Nuevo León, Mexico: Monterrey and rural Nuevo León, Hum. Immunol. 81 (2020) 516–518, https://doi.org/10.1016/j.humimm.2019.06.003.
[57] A. Bravo-Acevedo, R. Barquera, E. Arrieta-Bolaños, D.I. Hernández-Zaragoza, S. Clayton, I. Goné-Vázquez, et al., Genetic diversity of HLA system in a population sample from Aguascalientes, Mexico, Hum. Immunol. 81 (2020) 519–521, https://doi.org/10.1016/j.humimm.2019.05.016.
[58] J.C. Martínez-Álvarez, R. Barquera, D.I. Hernández-Zaragoza, A. Bravo-Acevedo, S. Clayton, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Querétaro, Mexico: Querétaro city and rural Querétaro, Hum. Immunol. 81 (2020) 522–524, https://doi.org/10.1016/j.humimm.2019.07.296.
[59] T.J. Rodríguez-Munguía, R. Barquera, C. Adalid-Sáinz, D.I. Hernández-Zaragoza, E. Arrieta-Bolaños, S. Clayton, et al., Genetic diversity of HLA system in two populations from Tamaulipas, Mexico: Ciudad Victoria and rural Tamaulipas, Hum. Immunol. 81 (2020) 525–527, https://doi.org/10.1016/j.humimm.2019.07.288.
[60] D.I. Hernández-Zaragoza, T.J. Rodríguez-Munguía, R. Barquera, C. Adalid-Sáinz, E. Arrieta-Bolaños, S. Clayton, et al., Genetic diversity of HLA system in two populations from San Luis Potosí, Mexico: San Luis Potosí City and rural San Luis Potosí, Hum. Immunol. 81 (2020) 528–530, https://doi.org/10.1016/j.humimm.2019.07.291.
[61] R. Barquera, C. López-Gil, V. Acuña-Alonzo, M. del R. Vega-Martínez, T.J. Rodríguez-Munguía, J.C. Martínez-Álvarez, et al., Genetic diversity of HLA system in seven populations from Veracruz, Mexico: Veracruz city, Coatzacoalcos, Córdoba, Orizaba, Poza Rica, Xalapa and rural Veracruz, Hum. Immunol. 81 (2020) 531–534, https://doi.org/10.1016/j.humimm.2019.07.292.
[62] R. Barquera, J.C. Martínez-Álvarez, D.I. Hernández-Zaragoza, A. Bravo-Acevedo, F. Juárez-Nicolás, A.J. Arriaga-Perea, et al., Genetic diversity of HLA system in six populations from Mexico City Metropolitan Area, Mexico: Mexico City North, Mexico City South, Mexico City East, Mexico City West, Mexico City Center and rural Mexico City, Hum. Immunol. 81 (2020) 539–543, https://doi.org/10.1016/j.humimm.2019.07.297.
[63] M. de los Á. Pavón-Vargas, M.H. Crawford, R. Barquera, C. López Gil, E. Arrieta-Bolaños, S. Clayton, et al., Genetic diversity of HLA system in two populations from Tlaxcala, Mexico: Tlaxcala City and rural Tlaxcala, Hum. Immunol. 81 (2020) 544–546, https://doi.org/10.1016/j.humimm.2019.07.282.
[64] S. Clayton, R. Barquera, M.G. Uribe-Duarte, I. Goné Vázquez, J. Zúñiga, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Sinaloa, Mexico: Culiacán and rural Sinaloa, Hum. Immunol. 81 (2020) 482–484, https://doi.org/10.1016/j.humimm.2019.06.006.

[65] C. López Gil, R. Barquera, M. de los Á. Pavón-Vargas, F. del R. Ramos-de la Cruz, P. Méndez-Mani, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Puebla, Mexico: Puebla city and rural Puebla, Hum. Immunol. 81 (2020) 547–549, https://doi.org/10.1016/j.humimm.2019.07.290.
[66] F. Juárez-Nicolás, R. Barquera, J.C. Martínez-Álvarez, D.I. Hernández-Zaragoza, A. Ortega-Yáñez, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in a population from Guerrero, Mexico, Hum. Immunol. 81 (2020) 550–552, https://doi.org/10.1016/j.humimm.2019.05.015.
[67] O. Hernández-Hernández, D.I. Hernández-Zaragoza, R. Barquera, C. Warinner, C. López-Gil, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Oaxaca, Mexico: Oaxaca city and rural Oaxaca, Hum. Immunol. 81 (2020) 553–556, https://doi.org/10.1016/j.humimm.2019.07.278.
[68] A. Ortega-Yáñez, R. Barquera, L. Curiel-Giles, J.C. Martínez-Álvarez, R.M. Macías-Medrano, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Morelos, Mexico: Cuernavaca and rural Morelos, Hum. Immunol. 81 (2020) 557–559, https://doi.org/10.1016/j.humimm.2019.07.289.
[69] R. Solís-Martínez, R. Barquera, K.S. Ponnandai-Shanmugavel, M. del R. Vega-Martínez, T.V. Vázquez-Castillo, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Tabasco, Mexico: Villahermosa and rural Tabasco, Hum. Immunol. 81 (2020) 560–562, https://doi.org/10.1016/j.humimm.2019.07.286.
[70] R. Barquera, F. Juárez-Nicolás, J.C. Martínez-Álvarez, K.S. Ponnandai-Shanmugavel, D.I. Hernández-Zaragoza, T.V. Vázquez-Castillo, et al., Genetic diversity of HLA system in two populations from Chiapas, Mexico: Tuxtla Gutiérrez and rural Chiapas, Hum. Immunol. 81 (2020) 563–565, https://doi.org/10.1016/j.humimm.2019.07.285.
[71] R. Barquera, J. Lara-Riegos, K.S. Ponnandai-Shanmugavel, A. Immel, E. Arrieta-Bolaños, S. Clayton, et al., Genetic diversity of HLA system in two populations from Campeche, Mexico: Campeche city and rural Campeche, Hum. Immunol. 81 (2020) 566–568, https://doi.org/10.1016/j.humimm.2019.07.281.
[72] J. Lara-Riegos, R. Barquera, O. del Castillo-Chávez, C.E. Medina-Escobedo, D.I. Hernández-Zaragoza, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Yucatán, Mexico: Mérida and rural Yucatán, Hum. Immunol. 81 (2020) 569–572, https://doi.org/10.1016/j.humimm.2019.07.280.
[73] C.E. Medina-Escobedo, R. Barquera, K.S. Ponnandai-Shanmugavel, J. Lara-Riegos, A. Bravo-Acevedo, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Quintana Roo, Mexico: Cancún and rural Quintana Roo, Hum. Immunol. 81 (2020) 573–575, https://doi.org/10.1016/j.humimm.2019.07.279.
[74] R. Barquera, J.C. Martínez-Álvarez, A.V. Trejo-Ordoz, M. de los Á. Pavón-Vargas, M. del R. Vega-Martínez, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Hidalgo, Mexico: Pachuca and rural Hidalgo, Hum. Immunol. 81 (2020) 535–538, https://doi.org/10.1016/j.humimm.2019.07.293.
[75] H. Pacheco-Ubaldo, C. Adalid-Sáinz, R. Barquera, S. Clayton, E. Arrieta-Bolaños, H. Delgado-Aguirre, et al., Genetic diversity of HLA system in three populations from Chihuahua, Mexico: Chihuahua City, Ciudad Juárez and rural Chihuahua, Hum. Immunol. 81 (2020) 485–488, https://doi.org/10.1016/j.humimm.2019.05.014.
[76] L. González-Medina, R. Barquera, H. Delgado-Aguirre, S. Clayton, C. Adalid-Sáinz, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in two populations from Durango, Mexico: Durango city and rural Durango, Hum. Immunol. 81 (2020) 489–491, https://doi.org/10.1016/j.humimm.2019.06.005.
[77] C. Adalid-Sáinz, R. Barquera, M.H. Crawford, A. Lona-Sánchez, S. Clayton, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in three populations from Coahuila, Mexico: Torreón, Saltillo and rural Coahuila, Hum. Immunol. 81 (2020) 492–495, https://doi.org/10.1016/j.humimm.2019.07.284.
[78] D.I. Hernández-Zaragoza, H. Delgado-Aguirre, R. Barquera, C. Adalid-Sáinz, S. Clayton, A. Lona-Sánchez, et al., Genetic diversity of HLA system in three populations from Zacatecas, Mexico: Zacatecas city, Fresnillo and rural Zacatecas, Hum. Immunol. 81 (2020) 496–498, https://doi.org/10.1016/j.humimm.2019.01.007.
[79] I. Goné-Vázquez, R. Barquera, F.P. Arellano-Prado, D.I. Hernández-Zaragoza, A. Escobedo-Ruíz, S. Clayton, et al., Genetic diversity of HLA system in two populations from Nayarit, Mexico: Tepic and rural Nayarit, Hum. Immunol. 81 (2020) 499–501, https://doi.org/10.1016/j.humimm.2019.06.008.
[80] A. Bravo-Acevedo, A. Escobedo-Ruíz, R. Barquera, S. Clayton, V.E. García-Arias, E. Arrieta-Bolaños, et al., Genetic diversity of HLA system in six populations from Jalisco, Mexico: Guadalajara city, Tlajomulco, Tlaquepaque, Tonalá, Zapopan and rural Jalisco, Hum. Immunol. 81 (2020) 502–505, https://doi.org/10.1016/j.humimm.2019.05.012.
[81] M. Ballesteros-Romero, R. Barquera, M.E. Rodríguez-López, D.I. Hernández-Zaragoza, I. Goné-Vázquez, S. Clayton, et al., Genetic diversity of HLA system in two populations from Michoacán, Mexico: Morelia and rural Michoacán, Hum. Immunol. 81 (2020) 506–509, https://doi.org/10.1016/j.humimm.2019.05.017.
[82] J. Fernández-Torres, D. Flores-Jiménez, A. Arroyo-Pérez, J. Granados, A. López-Reyes, HLA-B*40 allele plays a role in the development of Acute Leukemia in Mexican population: a case-control study, Biomed Res. Int. 2013 (2013) 705862.
[83] A. Ortega-Yáñez, Determinación de frecuencias alélicas y haplotípicas del sistema HLA en receptores y donadores en protocolo de trasplante renal y en protocolo de donador fallecido de la UMAE HE CMN sXXI del Servicio de Trasplantes y Nefrología de 2005 a 2011, Universidad Nacional Autónoma de México (UNAM), Mexico, 2012.
[84] J. Zúñiga, N. Yu, R. Barquera, S. Alosco, M. Ohashi, T. Lebedeva, et al., HLA Class I and Class II conserved extended haplotypes and their fragments or blocks in Mexicans: implications for the study of genetic diversity in admixed populations, PLoS ONE 8 (2013).
[85] American Board of Histocompatibility and Immunogenetics, ABHI Candidate Handbook, American Board of Histocompatibility and Immunogenetics, Lenexa, 2009.
[86] X. Zheng, J. Shen, C. Cox, J.C. Wakefield, M.G. Ehm, M.R. Nelson, et al., HIBAG-HLA genotype imputation with attribute bagging, Pharmacogenomics J. 14 (2014) 192–200, https://doi.org/10.1038/tpj.2013.18.
[87] J. Robinson, J.A. Halliwell, J.D. Hayhurst, P. Flicek, P. Parham, S.G.E. Marsh, The IPD and IMGT/HLA database: allele variant databases, Nucleic Acids Res. 43 (2015) D423–D431, https://doi.org/10.1093/nar/gku1161.
[88] S.G.E. Marsh, E.D. Albert, W.F. Bodmer, R.E. Bontrop, B. Dupont, H.A. Erlich, et al., An update to HLA Nomenclature, 2010, Bone Marrow Transplant. 45 (2010) 846–848, https://doi.org/10.1038/bmt.2010.79.
[89] R. Holdsworth, C.K. Hurley, S.G.E. Marsh, M. Lau, H.J. Noreen, J.H. Kempenich, et al., The HLA dictionary 2008: A summary of HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1 alleles and their association with serologically defined HLA-A, -B, -C, -DR, and -DQ antigens, Tissue Antigens. 73 (2009) 95–170. doi:10.1111/j.1399-0039.2008.01183.x.
[90] L. Excoffier, H.E.L. Lischer, Arlequin suite ver 3.5: a new series of programs to perform population genetics analyses under Linux and Windows, Mol. Ecol. Resour. 10 (2010) 564–567, https://doi.org/10.1111/j.1755-0998.2010.02847.x.
[91] E.J. Yunis, C.E. Larsen, M. Fernandez-Viña, Z.L. Awdeh, T. Romero, J.A. Hansen, et al., Inheritable variable sizes of DNA stretches in the human MHC: conserved extended haplotypes and their fragments or blocks, Tissue Antigens 62 (2003) 1–20, https://doi.org/10.1034/j.1399-0039.2003.00098.x.
[92] E.J. Yunis, J. Zuñiga, C.E. Larsen, C.A. Alper, Z.L. Awdeh, M. Fernández-Viña, et al., Single nucleotide polymorphism blocks and haplotypes: human MHC block diversity, Encycl. Mol. Cell Biol. Mol. Med. 13 (2006) 192–215, https://doi.org/10.1002/3527600906.mcb.200500062.
[93] E. Arrieta-Bolaños, J.J. Madrigal-Sánchez, J.E. Stein, P. Órlich-Pérez, M.J. Moreira-Espinoza, E. Paredes-Carias, et al., High-resolution HLA allele and haplotype frequencies in majority and minority populations of Costa Rica and Nicaragua: Differential admixture proportions in neighboring countries, HLA. 91 (2018) 514–529, https://doi.org/10.1111/tan.13280.
[94] L. Gragert, A. Madbouly, J. Freeman, M. Maiers, Six-locus high resolution HLA haplotype frequencies derived from mixed-resolution DNA typing for the entire US donor registry, Hum. Immunol. 74 (2013) 1313–1320, https://doi.org/10.1016/j.humimm.2013.06.025.
[95] O.D. Solberg, S.J. Mack, A.K. Lancaster, R.M. Single, Y. Tsai, A. Sanchez-Mazas, et al., Balancing selection and heterogeneity across the classical human leukocyte antigen loci: a meta-analytic review of 497 population studies, Hum. Immunol. 69 (2008) 443–464, https://doi.org/10.1016/j.humimm.2008.05.001.
[96] F. Vogel, A.G. Motulsky, Human Genetics: Problems and Approaches, third ed., Springer, New York, 1997.
[97] J. Wang, Maximum-likelihood estimation of admixture proportions from genetic data, Genetics 164 (2003) 747–765, https://doi.org/10.1111/J.1474-919X.2005.00468.X.
[98] R.G. Newcombe, D.G. Altman, Proportions and their differences, in: D.G. Altman, D. Machin, T.N. Bryant, M.J. Gardner (Eds.), Stat. with Confid., 2nd ed, BMJ Books, Bristol, 2000: pp. 45–56.
[99] I. Campbell, Chi-squared and Fisher – Irwin tests of two-by-two tables with small sample recommendations, (2007) 3661–3675. doi:10.1002/sim.
[100] R. Bender, S. Lange, Adjusting for multiple testing – when and how? J. Clin. Epidemiol. 54 (2001) 343–349, https://doi.org/10.1016/S0895-4356(00)00314-0.
[101] E.D. Juárez Cortés, M.A. Sieck Contreras, A.J. Arriaga Perea, R.M. Macías Medrano, A. Balbuena Jaime, P. Everardo Martínez, et al., Genetic differentiation in a sample from northern Mexico city detected by HLA system analysis: Impact in the study of population immunogenetics, Hum. Biol. 89 (2017) 181–193, https://doi.org/10.13110/humanbiology.89.3.02.
[102] J.M. Galarza, R. Barquera, A.M.T. Álvarez, D.I. Hernández Zaragoza, G. Peralta Sevilla, A. Tamayo, et al., Genetic diversity of the HLA system in human populations from the Sierra (Andean), Oriente (Amazonian) and Costa (Coastal) regions of Ecuador, Hum. Immunol. 79 (2018) 639–650, https://doi.org/10.1016/j.humimm.2018.06.004.
[103] F. Manni, E. Guérard, H. Evelyne, Geographic patterns of (genetic, morphologic, linguistic) variation: how barriers can be detected by using Monmonier's algorithm, Hum. Biol. 76 (2004) 173–190 http://www.jstor.org/stable/41466226.
[104] N. Takezaki, M. Nei, K. Tamura, POPTREEW: Web version of POPTREE for constructing population trees from allele frequency data and computing some other quantities, Mol. Biol. Evol. 31 (2014) 1622–1624, https://doi.org/10.1093/molbev/msu093.
[105] M. Nei, Estimation of average heterozygosity and genetic distance from a small number of individuals, Genetics 89 (1978) 583–590, https://doi.org/10.3390/ijms15010277.
[106] N. Masatoshi, Molecular Evolutionary Genetics, reprint, Columbia University Press, New York, 1987.
[107] M. Raymond, F. Rousset, An Exact Test for Population Differentiation, Evolution (N. Y). 49 (1995) 1280–1283.
[108] J. Goudet, M. Raymond, T. De Meeüs, F. Rousset, Testing differentiation in diploid populations, Genetics 144 (1996) 1933–1940, https://doi.org/10.1111/j.1471-8286.2007.01769.x.
[109] L. Excoffier, L. Guillaume, S. Stefan, Arlequin (version 3.0): an integrated software package for population genetics data analysis., Evol. Bioinform. Online. 1 (2005) 47–50. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2658868%5C&tool=pmcentrez%5C&rendertype=abstract.
[110] N. Yasuda, HLA polymorphism information content (PIC), Jinrui Idengaku Zasshi

33 (1988) 385–387.
[111] C. Yan, R. Wang, J. Li, Y. Deng, D. Wu, H. Zhang, et al., HLA-A gene polymorphism defined by high-resolution sequence-based typing in 161 Northern Chinese Han people., Genomics, Proteomics Bioinforma. / Beijing Genomics Inst. 1 (2003) 304–309. doi:10.1016/S1672-0229(03)01036-2.
[112] C.M. Shen, B.F. Zhu, Y.J. Deng, S.H. Ye, J.W. Yan, G. Yang, et al., Allele polymorphism and haplotype diversity of HLA-A, -B and -DRB1 loci in sequence-based typing for Chinese Uyghur ethnic group, PLoS ONE 5 (2010), https://doi.org/10.1371/journal.pone.0013458.
[113] J.E. García-Ortiz, L. Sandoval-Ramírez, H. Rangel-Villalobos, H. Maldonado-Torres, S. Cox, C.A. García-Sepúlveda, et al., High-resolution molecular characterization of the HLA class I and class II in the Tarahumara Amerindian population, Tissue Antigens 68 (2006) 135–146, https://doi.org/10.1111/j.1399-0039.2006.00636.x.
[114] F. Loeza, G. Vargas-Alarcón, F. Andrade, Y. Vergara, J. Rodríguez-Pérez, J.A. Ruiz-Morales, et al., Distribution of class I and class III MHC antigens in the Tarasco Amerindians, Hum. Immunol. 63 (2002) 143–148, https://doi.org/10.1016/S0198-8859(01)00371-8.
[115] E. Infante, C. Aláez, H. Flores, C. Gorodezky, Seri from Sonora, Mexico. Anthropology/human genetic diversity population reports, in: J.A. Hansen (Ed.), Immunobiol. Hum. MHC Proc. 13th Int. Histocompat. Work. Conf. Vol. I, IHWG Press, Seattle, 2007: pp. 633–634.
[116] H.A. Erlich, 13th international histocompatibility workshop Anthropology/Human genetic diversity joint report: HLA genetic differentiation of the 13th IHWC population data relative to worldwide linguistic families, in: J.A. Hansen (Ed.), Immunobiol. Hum. MHC Proc. 13th Int. Histocompat. Work. Conf. Vol. I, IHWG Press, Seattle, 2006: pp. 758–766.
[117] R. Williams, Y.F. Chen, R. Endres, D. Middleton, M. Trucco, J.D. Williams, et al., Molecular variation at the HLA-A, B, C, DRB1, DQA1, and DQB1 loci in full heritage American Indians in Arizona: Private haplotypes and their evolution, Tissue Antigens 74 (2009) 520–533, https://doi.org/10.1111/j.1399-0039.2009.01381.x.
[118] M.S. Leffell, M.D. Fallin, W.H. Hildebrand, J.W. Cavett, B.A. Iglehart, A.A. Zachary, HLA alleles and haplotypes among the lakota sioux: report of the ASHI minority workshops, part III, Hum. Immunol. 65 (2004) 78–89, https://doi.org/10.1016/j.humimm.2003.10.001.
[119] E.A. Trachtenberg, H.A. Erlich, O. Rickards, G.F. DeStefano, W. Klitz, HLA class II linkage disequilibrium and haplotype evolution in the Cayapa Indians of Ecuador, Am J Hum Genet. 57 (1995) 415–424.
[120] A. Arnaiz-Villena, V. Gonzalez-Alcos, J.I. Serrano-Vela, R. Reguera, L. Barbolla, C. Parga-Lozano, et al., HLA genes in Uros from Titikaka Lake, Peru: Origin and relationship with other Amerindians and worldwide populations, Int. J. Immunogenet. 36 (2009) 159–167, https://doi.org/10.1111/j.1744-313X.2009.00841.x.
[121] A. Arnaiz-Villena, N. Siles, J. Moscoso, J. Zamora, J.I. Serrano-Vela, E. Gomez-Casado, et al., Origin of Aymaras from Bolivia and their relationship with other Amerindians according to HLA genes, Tissue Antigens 65 (2005) 379–390, https://doi.org/10.1111/j.1399-0039.2005.00356.x.
[122] G. Vargas-Alarcon, J. Moscoso, J. Martinez-Laso, J.M. Rodriguez-Perez, C. Flores-Dominguez, J.I. Serrano-Vela, et al., Origin of Mexican Nahuas (Aztecs) according to HLA genes and their relationships with worldwide populations, Mol. Immunol. 44 (2007) 747–755, https://doi.org/10.1016/j.molimm.2006.04.014.
[123] G. Vargas-Alarcon, G. Hernandez-Pacheco, J. Zuniga, J.M. Rodriguez-Perez, N. Perez-Hernandez, C. Rangel, et al., Distribution of HLA-B alleles in Mexican Amerindian populations, Immunogenetics 54 (2003) 756–760, https://doi.org/10.1007/s00251-002-0522-0.
[124] A. Arnaiz-Villena, G. Vargas-Alarcón, C. Areces, M. Enríquez-de-Salamanca, S. Abd-El-Fatah-Khalil, M. Fernández-Honrado, et al., Mixtec Mexican Amerindians: An HLA Alleles study for America peopling, pharmacogenomics and transplantation, Immunol. Invest. 43 (2014) 738–755, https://doi.org/10.3109/08820139.2014.926369.
[125] M.S. Leffell, M.D. Fallin, H.A. Erlich, M. Fernandez-Vīna, W.H. Hildebrand, S.J. Mack, et al., HLA antigens, alleles and haplotypes among the Yup'ik Alaska natives: report of the ASHI Minority Workshops, part II, Hum. Immunol. 63 (2002) 614–625, https://doi.org/10.1016/S0198-8859(02)00415-9.
[126] J. Martinez-Laso, N. Siles, J. Moscoso, J. Zamora, J.I. Serrano-Vela, J.I. R-A-Cachafeiro, et al., Origin of Bolivian Quechua Amerindians: Their relationship with other American Indians and Asians according to HLA genes, Eur. J. Med. Genet. 49 (2006) 169–185. doi:10.1016/j.ejmg.2005.04.005.
[127] G. Vargas-Alarcón, G. Hernández-Pacheco, J. Moscoso, N. Pérez-Hernández, L.E. Murguía, A. Moreno, et al., HLA genes in Mexican Teeneks: HLA genetic relationship with other worldwide populations, Mol. Immunol. 43 (2006) 790–799, https://doi.org/10.1016/j.molimm.2005.07.017.
[128] A. Arnaiz-Villena, S. Abd-El-Fatah, M.A. Granados-Silvestre, C. Parga-Lozano, P. Gómez-Prieto, D. Rey, et al., Human leukocyte antigen-DRB1 Class II Genes in Mexican Amerindian Mazahuas: genes and languages do not correlate, Genet. Test. Mol. Biomarkers. 15 (2011) 97–102, https://doi.org/10.1089/gtmb.2010.0055.
[129] E. Gómez-Casado, J. Martínez-Laso, J. Moscoso, J. Zamora, M. Martin-Villa, M. Perez-Blas, et al., Origin of Mayans according to HLA genes and the uniqueness of Amerindians, Tissue Antigens 61 (2003) 425–436, https://doi.org/10.1034/j.1399-0039.2003.00040.x.
[130] L.T. Tsuneto, C.M. Probst, M.H. Hutz, F.M. Salzano, L.A. Rodriguez-Delfin, M.A. Zago, et al., HLA class II diversity in seven Amerindian populations. Clues about the origins of the Aché, Tissue Antigens 62 (2003) 512–526, https://doi.org/10.1046/j.1399-0039.2003.00139.x.
[131] A. Trachtenberg, J.E. Bernal, M.C. Rhodas, H.A. Erlich, Results of Expedicion Humana. I. Analysis of HLA class I1 (DRB 1-DQA1-DQB 1-DPB 1) alleles and DR-DQ haplotypes in nine Amerindian populations from Colombia, Tissue Antigens (1996) 174–181.
[132] A. Arnaiz-Villena, G. Vargas-Alarcón, J. Granados, E. Gómez-Casado, J. Longas, M. Gonzalez-Hevilla, et al., HLA genes in Mexican Mazatecans, the peopling of the Americas and the uniqueness of Amerindians, Tissue Antigens 56 (2000) 405–416, https://doi.org/10.1034/j.1399-0039.2000.560503.x.
[133] E.A. Titus-Trachtenberg, O. Rickards, G.F. De Stefano, H.A. Erlich, Analysis of HLA class II haplotypes in the Cayapa Indians of Ecuador: a novel DRB1 allele reveals evidence for convergent evolution and balancing selection at position 86, Am. J. Hum. Genet. 55 (1994) 160–167.
[134] M.V. Monsalve, G. Edin, D.V. Devine, Analysis of HLA class I and class II of Na-Dene and Amerindian populations from British Columbia, Canada, Hum. Immunol. 59 (1998) 48–55, https://doi.org/10.1016/S0198-8859(97)00251-6.
[135] A. Dafalla, Sample of mixed population from Shaigiya, Sudan, in: D. Charron (Ed.), 12th Int. Histocompat. Work. - HLA, EDK, St. Malo, 1997.
[136] A.M. Dafalla, D.J. McCloskey, A.A. Alemam, A.A. Ibrahim, A.M. Babikir, N. Gasmelseed, et al., HLA Polymorphism in Sudanese Renal Donors, Saudi J. Kidney Dis. Transplant. 22 (2011) 834–840.
[137] D. Modiano, G. Luoni, V. Petrarca, B. Sodiomon Sirima, M. De Luca, J. Simporé, et al., HLA class I in three West African ethnic groups: Genetic distances from sub-Saharan and Caucasoid populations, Tissue Antigens. 57 (2001) 128–137. doi:10.1034/j.1399-0039.2001.057002128.x.
[138] P. Lulli, V.D. Mangano, A. Onori, C. Batini, G. Luoni, B.S. Sirima, et al., HLA-DRB1 and -DQB1 loci in three west African ethnic groups: genetic relationship with sub-Saharan African and European populations, Hum. Immunol. 70 (2009) 903–909, https://doi.org/10.1016/j.humimm.2009.07.025.
[139] Z. Li, D. Chen, C. Zhang, Y. Li, B. Cao, T. Ning, et al., HLA polymorphisms are associated with Helicobacter pylori infected gastric cancer in a high risk population, China, Immunogenetics 56 (2005) 781–787, https://doi.org/10.1007/s00251-004-0723-9.
[140] S. Jasti, S. Rakh, V. Pantula, K.J.R. Murthy, V.L. Valluri, Genetic affinity of two south Indian ethnic groups with other populations, Int. J. Immunogenet. 35 (2008) 243–249, https://doi.org/10.1111/j.1744-313X.2008.00763.x.
[141] M.E. Ali, M.U. Ahmed, S. Alam, M.H. Rahman, HLA-A, -B and -DRB1 allele frequencies in the Bangladeshi population, Tissue Antigens 72 (2008) 115–119, https://doi.org/10.1111/j.1399-0039.2008.01079.x.
[142] C. Crespí, J. Milà, N. Martínez-Pomar, A. Etxagibel, I. Muñoz-Saa, D. Priego, et al., HLA polymorphism in a Majorcan population of Jewish descent: comparison with Majorca, Minorca, Ibiza (Balearic Islands) and other Jewish communities, Tissue Antigens 60 (2002) 282–291.
[143] A. Mas, E. Blanco, G. Moñux, E. Urcelay, F.J. Serrano, E.G. De La Concha, et al., DRB1-TNF-α-TNF-β haplotype is strongly associated with severe aortoiliac occlusive disease, a clinical form of atherosclerosis, Hum. Immunol. 66 (2005) 1062–1067, https://doi.org/10.1016/j.humimm.2005.10.001.
[144] J. Pingel, U.V. Solloch, J.A. Hofmann, V. Lange, G. Ehninger, A.H. Schmidt, High-resolution HLA haplotype frequencies of stem cell donors in Germany with foreign parentage: how can they be used to improve unrelated donor searches? Hum. Immunol. 74 (2013) 330–340, https://doi.org/10.1016/j.humimm.2012.10.029.
[145] S. Rendine, N.M. Ferrero, N. Sacchi, C. Costa, S. Pollichieni, A. Amoroso, Estimation of human leukocyte antigen class I and class II high-resolution allele and haplotype frequencies in the Italian population and comparison with other European populations, Hum. Immunol. 73 (2012) 399–404, https://doi.org/10.1016/j.humimm.2012.01.005.
[146] E. Arrieta-Bolaños, H. Maldonado-Torres, O. Dimitriu, M.A. Hoddinott, F. Fowles, A. Shah, et al., HLA-A, -B, -C, -DQB1, and -DRB1,3,4,5 allele and haplotype frequencies in the Costa Rica Central Valley Population and its relationship to worldwide populations, Hum. Immunol. 72 (2011) 80–86, https://doi.org/10.1016/j.humimm.2010.10.005.
[147] I.A. Páez-Gutiérrez, Colombia Bogota Cord Blood, Allele Freq. Worldw. Popul. (2017). http://allelefrequencies.net/hla6003a.asp?hla_locus1=&hla_locus2=&hla_locus3=&hla_locus4=&hla_locus5=&hla_locus6=&hla_locus7=&hla_locus8=&hla_population=3568&hla_country=&hla_dataset=&hla_region=&hla_ethnic=&hla_study=&hla_order=order_3&hla_sample_size_pa (accessed December 19, 2018).
[148] L. Torres, HLA-A, -B, -DRB1 allele and haplotype frequencies of 8.432 Cord Blood Units from the Southeast Region of Brazil, Allele Freq. Worldw. Popul. (2016). http://allelefrequencies.net/hla6003a.asp?hla_locus1=&hla_locus2=&hla_locus3=&hla_locus4=&hla_locus5=&hla_locus6=&hla_locus7=&hla_locus8=&hla_population=3566&hla_country=&hla_dataset=&hla_region=&hla_ethnic=&hla_study=&hla_order=order_3&hla_sample_size_pa (accessed December 19, 2018).
[149] R. Alegre, J. Moscoso, J. Martinez-Laso, M. Martin-Villa, J. Suarez, A. Moreno, et al., HLA genes in Cubans and the detection of Amerindian alleles, Mol. Immunol. 44 (2007) 2426–2435, https://doi.org/10.1016/j.molimm.2006.10.017.
[150] C. Schäfer, J. Sauter, T. Riethmüller, Z.M. Kashi, A.H. Schmidt, F.J. Barriga, HLA-A, -B, -DRB1 allele and haplotype frequencies of 920 cord blood units from Central Chile, Hum. Immunol. 77 (2016) 622–623, https://doi.org/10.1016/j.humimm.2016.05.020.
[151] J. Martinez-Laso, F. Montoya, C. Areces, J. Moscoso, C. Silvera, D. Rey, et al., HLA in Jaidukama: An Amerindian secluded Colombian population with new haplotypes and Asian and Pacific-shared alleles, Mol. Biol. Rep. 38 (2011) 3689–3701, https://doi.org/10.1007/s11033-010-0483-6.
[152] Z. Layrisse, Y. Guedez, E. Domínguez, N. Paz, S. Montagnani, M. Matos, et al., Extended HLA haplotypes in a Carib Amerindian population: the Yucpa of the

Perija Range, Hum. Immunol. 62 (2001) 992–1000, https://doi.org/10.1016/S0198-8859(01)00297-X.
[153] R. Barquera, J. Zúñiga, R. Hernández-Díaz, V. Acuña-Alonzo, K. Montoya-Gama, J. Moscoso, et al., HLA class I and class II haplotypes in admixed families from several regions of Mexico, Mol. Immunol. 45 (2008) 1171–1178, https://doi.org/10.1016/j.molimm.2007.07.042.
[154] R. Barquera, V. Acuña-Alonzo, C. López-Gil, C. Adalid-Sáinz, M. del R. Vega-Martínez, F. Juárez-Nicolás, et al., Una primera aproximación a la generación de un mapa inmunogenético de la población mexicana, Estud. Antropol. Biológica. XVII (2014) 77–91.
[155] R. Barquera, J. Granados, La diversidad en los haplotipos del sistema HLA en las poblaciones mestizas de México, Cuicuilco 20 (2013) 196–226.
[156] W. Klitz, L. Gragert, M. Maiers, B. Tu, A. Lazaro, R. Yang, et al., Four locus high resolution HLA typing in a sample of Mexican Americans, Tissue Antigens 74 (2009) 508–513, https://doi.org/10.1111/j.1399-0039.2009.01374.x.Four.
[157] T.M. Ruiz, S.M.C.M. Da Costa, F. Ribas, P.R. Luz, S.S. Lima, M. Da, Graça Bicalho, Human leukocyte antigen allelic groups and haplotypes in a Brazilian sample of volunteer donors for bone marrow transplant in Curitiba, Paraná, Brazil, Transplant. Proc. 37 (2005) 2293–2296, https://doi.org/10.1016/j.transproceed.2005.03.036.
[158] C. Kollman, M. Maiers, L. Gragert, C. Müller, M. Setterholm, M. Oudshoorn, et al., Estimation of HLA-A, -B, -DRB1 Haplotype Frequencies Using Mixed Resolution Data from a National Registry with Selective Retyping of Volunteers, Hum. Immunol. 68 (2007) 950–958, https://doi.org/10.1016/j.humimm.2007.10.009.
[159] I. Silva-Zolezzi, A. Hidalgo-Miranda, J. Estrada-Gil, J.C. Fernandez-Lopez, L. Uribe-Figueroa, A. Contreras, et al., Analysis of genomic diversity in Mexican Mestizo populations to develop genomic medicine in Mexico, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 8611–8616.
[160] D.M. Hanratty, The society and its environment, in: T. Merrill, R. Miró (Eds.), Mex. a Ctry. Study, 4th ed., Library of Congress. Federal Research Division, Washington, D.C., 1997: pp. 77–140.
[161] P. Martínez, M. Á. y García, J. E. y Fernández, Indígenas en zonas metropolitanas, La Situación Demográfica En México. (2003) 1–10. http://www.conapo.gob.mx/publicaciones/sdm/sdm2003/11.pdf.
[162] J.J. Chen, J.A. Hollenbach, E.A. Trachtenberg, J.J. Just, M. Carrington, K.S. Rønningen, et al., Hardy-Weinberg testing for HLA class II (DRB1, DQA1, DQB1, AND DPB1) loci in 26 human ethnic groups, Tissue Antigens 54 (1999) 533–542, https://doi.org/10.1034/j.1399-0039.1999.540601.x.
[163] D. Meyer, V.R. Vitor, B.D. Bitarello, D.Y. Débora, K. Nunes, A genomic perspective on HLA evolution, Immunogenetics 70 (2018) 5–27, https://doi.org/10.1007/s00251-017-1017-3.
[164] J. Lindo, E. Huerta-Sánchez, S. Nakagome, M. Rasmussen, B. Petzelt, J. Mitchell, et al., A time transect of exomes from a Native American population before and after European contact, Nat. Commun. 7 (2016), https://doi.org/10.1038/ncomms13175.
[165] S. Mallal, E. Phillips, G. Carosi, J.-M. Molina, C. Workman, J. Tomažič, et al., HLA-B*5701 Screening for Hypersensitivity to Abacavir, N. Engl. J. Med. (2009), https://doi.org/10.1056/NEJMOA0706135.
[166] I. Fricke-Galindo, A. Llerena, M. López-López, An update on HLA alleles associated with adverse drug reactions, Drug Metab. Pers. Ther. 32 (2017) 73–87, https://doi.org/10.1515/dmpt-2016-0025.
[167] K.S. Lim, P. Kwan, C.T. Tan, Association of HLA-B * 1502 allele and carbamazepine- induced severe adverse cutaneous drug reaction among Asians , a review, Neurol. Asia. 13 (2008) 15–21. https://www.researchgate.net/publication/266403328_Association_of_HLA-B1502_allele_and_carbamazepine-induced_severe_adverse_cutaneous_drug_reaction_among_Asians_a_review.
[168] N. Kaniwa, Y. Saito, The risk of cutaneous adverse reactions among patients with the HLA-A* 31: 01 allele who are given carbamazepine, oxcarbazepine or eslicarbazepine: a perspective review, Ther. Adv. Drug Saf. 4 (2013) 246–253, https://doi.org/10.1177/2042098613499791.
[169] U. Amstutz, C.J.D. Ross, L.I. Castro-Pastrana, M.J. Rieder, N.H. Shear, M.R. Hayden, et al., HLA-A*31:01 and HLA-B*15:02 as genetic markers for carbamazepine hypersensitivity in children, Clin. Pharmacol. Ther. 94 (2013) 142–149, https://doi.org/10.1038/clpt.2013.55.
[170] H.Y. Sun, C.C. Hung, P.H. Lin, S.F. Chang, C.Y. Yang, S.Y. Chang, et al., Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan, J. Antimicrob. Chemother. 60 (2007) 599–604, https://doi.org/10.1093/jac/dkm243.
[171] A.M. Martin, D. Nolan, S. Gaudieri, C.A. Almeida, R. Nolan, I. James, et al., Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant, Proc. Natl. Acad. Sci. 101 (2004) 4180–4185, https://doi.org/10.1073/pnas.0307067101.
[172] A.K. Daly, P.T. Donaldson, P. Bhatnagar, Y. Shen, I. Pe'Er, A. Floratos, et al., HLA-B5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin, Nat. Genet. 41 (2009) 816–819. doi:10.1038/ng.379.
[173] A. Alfirevic, F. Gonzalez-Galarza, C. Bell, K. Martinsson, V. Platt, G. Bretland, et al., In silico analysis of HLA associations with drug-induced liver injury: Use of a HLA-genotyped DNA archive from healthy volunteers, Genome Med. 4 (2012) 51, https://doi.org/10.1186/gm350.
[174] Secretaría de Salud, Guía de Referencia Rápida "Diagnóstico y Tratamiento del Síndrome de Stevens-Johnson /Necrólisis Epidérmica Tóxica en el adulto," Mexico City, 2011.
[175] Secretaría de Salud, Guía de Práctica Clínica Diagnóstico y Tratamiento del Síndrome de Stevens Johnson/Necrólisis Epidérmica Tóxica, Mexico City, 2011.
[176] H. Valenzuela-Ponce, S. Alva-Hernández, D. Garrido-Rodríguez, M. Soto-Nava, T. García-Téllez, T. Escamilla-Gómez, et al., Novel HLA class I associations with HIV-1 control in a unique genetically admixed population, Sci. Rep. 8 (2018) 1DUMMY. doi:10.1038/s41598-018-23849-7.
[177] D. Chessman, L. Kostenko, T. Lethborg, A.W. Purcell, N.A. Williamson, Z. Chen, et al., Human leukocyte antigen class I-restricted activation of CD8 + T cells provides the immunogenetic basis of a systemic drug hypersensitivity, Immunity 28 (2008) 822–832, https://doi.org/10.1016/j.immuni.2008.04.020.
[178] R.J. Duquesnoy, M. Askar, HLAMatchmaker: A Molecularly Based Algorithm for Histocompatibility Determination. V. Eplet Matching for HLA-DR, HLA-DQ, and HLA-DP, Hum. Immunol. 68 (2007) 12–25. doi:10.1016/j.humimm.2006.10.003.
[179] A. Sanchez-Mazas, D. Meyer, The relevance of HLA sequencing in population genetics studies, J. Immunol. Res. 2014 (2014), https://doi.org/10.1155/2014/971818.