

SUPPLEMENTARY METHODS

1. Selection of datasets and calculation of Weighted Allele Frequencies by country:

To calculate Weighted Allele Frequencies (WAFs) in the current and updated scenarios, we selected studies following the selection criteria described in the Methods section. As mentioned, some studies were not compatible, which led to few exceptions. For the sake of reproducibility, we are providing below the selection process in full detail. This is summarized in Table S3.

1.1 Current Scenario, collecting datasets in the AFNDB:

- **Argentina:**

Applying the auxiliary rule for HLA class I, we obtained two datasets of Fernández-Viña *et al.*, 1997 (1) (Toba: N = 84 for A and N = 116 for B, Wichí: N = 44 for A and N = 46 for B). And two datasets of Marcos, 2000 (Toba: N = 86 for A and B, and Chiriguano: N = 54 for A and B), unpublished but available in the AFNDB. Nevertheless, we did not consider Chiriguano (N = 54) because most alleles were characterized at 2-digit resolution and just a 3 were characterized at 4-digit resolution. There were no datasets with 4-digit resolution for HLA-I C. For HLA class II, we did not need to apply the auxiliary rule. We included the studies of Cerna *et al.*, 1993 (N = 116) (2) and Marcos, 2000 (N = 365) for DPB1, DQA1, DQB1 and DRB1. We did not include the study of Motta *et al.*, 2007 (3) for DQB1 because it did not resolve most of the alleles at 4-digit resolution.

- **Bolivia:**

For HLA-II we collected the datasets of Martínez-Laso *et al.*, 2006 (N = 80) (4) and Arnaiz-Villena *et al.*, 2005 (N = 102) (5), which report alleles of DRB1 with 4-digit resolution. There are no studies with 4-digit resolution for HLA class I. We are including the 2-digit resolution data of these two studies in Tables S4 and S5 just for illustrative purposes. These values were not used in any further analysis.

- **Brazil:**

We applied the auxiliary rule for HLA-I, including the datasets of Donadi, 2002 (N = 108, available in the AFNDB) and Nunes *et al.*, 2016 (N = 144) (6) for the genes A, B and C. Also, the datasets of Middleton *et al.*, 2000 (N = 95 for A) (7), Williams *et al.*, 2001 (N = 95 for B) (8) and Lazaro *et al.*, 1999 (N = 60 for A and N = 58 for B) (9).

For HLA class II, we applied the auxiliary rule for DPA1 and DPB1, including the datasets of Erlich, 2002 (N = 50, available in the AFNDB) for DPA1 and DPB1, and Cerna *et al.*, 1993 (N = 74) (2) for DPB1. We did not need to apply the auxiliary rule for DQA1, DQB1 and DRB1. For these 3 genes, we included the studies of Castillo Lima Vendramini *et al.*, 2020 (N = 641)

(10), Maciag *et al.*, 2019 (N = 205, data taken from the AFNDB) (11) and Tsuneto *et al.*, 2003, which reports two datasets (First dataset: N=160 for these 3 genes; Second dataset: N = 235 for DQA1 and DRB1, N = 209 for DQB1) (12). Also, Temin *et al.*, 2002 (N = 103, available in the AFNDB) for both DQB1 and DRB1. And the datasets reported by Piovezan *et al.*, 2019 (N = 203) (13), Donadi, 2002 (N = 108) and Nunes *et al.*, 2016 (N = 144) (6) for DRB1 only.

- Chile:

We did not find studies with 100 or more individuals for HLA class I. By applying the auxiliary rule, we obtained the datasets of Arnaiz-Villena *et al.*, 2019 (N = 66 for A and B) (14) and Turner *et al.*, 2005 (N = 70), only available in the AFNDB. For HLA class II, we used the two studies mentioned above and the datasets reported by Pérez-Bravo *et al.*, 1999 (N = 124, for DQA1 and DQB1) (15) and Schäfer *et al.*, 2016 (N = 920, DRB1) (16).

- Colombia:

For HLA-I, using our inclusion criteria, we only obtained the study of Páez-Gutiérrez *et al.*, 2019 (N = 1463) (17) for A, B and C. For HLA-II, we applied the auxiliary rule for DPB1 and DQA1, selecting the datasets of Briceno *et al.*, 1996 (N = 54) for DPB1 (18) and Yunis *et al.*, 1994 (19) for DQA1. From this last study, as just the number of alleles in each dataset were provided, we are using N = 61.5 and N = 55.5 as approximation of the sample sizes. Of note, the frequencies reported for DPB1 and DQA1 are based on specific ethnic groups and may not be representative of the country diversity.

For genes DQB1 and DRB1, we only included the study of Páez-Gutiérrez *et al.*, 2019 (N = 1463, PCR-SBT) (17) and not the studies of Correa *et al.*, 2002 (N = 100, PCR-SSP) (20) and Arnaiz-Villena *et al.*, 2018 (N = 188, PCR-SSOP) (21) due to big differences in sample size and superior resolution technology (22,23).

- Ecuador:

By applying the auxiliary rule for HLA-I A, we included the study of Arnaiz-Villena *et al.*, 2018 (N = 63) (24). For HLA-I B, we only considered the integrated dataset of Galarza *et al.*, 2018 (N = 1101) (25) and not its subpopulations, which are also available individually on the AFNDB. We did not find studies of HLA-I C meeting our inclusion criteria.

For HLA-II, we applied the auxiliary rule for genes DPA1, DPB1, DQA1 and DQB1. For DPA1, we only found the dataset reported by Begovich *et al.*, 2001 (N = 58, Ecuadorian African) (26). For DPB1, we are using the datasets of Begovich *et al.*, 2001 (N = 58, Ecuadorian African) (26) and Trachtenberg *et al.*, 1995 (N = 183, Cayapa), available in the AFNDB. This last dataset combines the samples reported by Begovich *et al.*, 2001 (N = 83, Cayapa) (26) and Trachtenberg *et al.*, 1995 (N = 100, Cayapa) (27).

For both DQA1 and DQB1, we considered the datasets of Begovich *et al.*, 2000 (N = 58, Ecuadorian African) (28) and Trachtenberg *et al.*, 1995 (N = 183, Cayapa), available in the AFNDB. This last merges the datasets published in Begovich *et al.*, 2000 (N = 83, Cayapa)

(28) and Trachtenberg *et al.*, 1995 (N=100, Cayapa) (27). For DRB1, we only obtained the dataset of Trachtenberg *et al.*, 1995 (N = 183), available only in the AFNDB.

- Paraguay:

We did not find any eligible dataset for HLA-I. By applying the auxiliary rule for HLA class II, we only obtained the dataset of Tsuneto *et al.*, 2003 (N = 87) (12) for DQA1, DQB1 and DRB1. Importantly, these HLA allelic frequencies came from to the Aché ethnic group and may not be representative of the country's diversity.

- Peru:

For HLA-I A and B, we only considered the dataset of Arnaiz-Villena *et al.*, 2009 (N = 105) (29), which is reported twice in the AFNDB. However, this comes from an ethnic group (Uros) and may not be representative of the country's diversity. We did not find any other eligible study, neither for HLA-I A, B, C nor HLA-II DQA1, even applying the auxiliary rule. For illustrative purposes only, we are showing the HLA-I C alleles at 2-digit resolution reported by de Pablo *et al.*, 2000 (N = 148) (30). We are using the dataset of Tsuneto *et al.*, 2003 (N = 44, Quechua) (12) for HLA-II DQA1 only and not for DRB1, because many HLAs were typified just at 2-digit resolution for this gene.

We applied the auxiliary rule for HLA-II DQB1 and DRB1, selecting the studies of Arnaiz-Villena *et al.*, 2009 (N = 105) (29) and Moscoso *et al.*, 2006 (N = 83) (31) for both genes; and de Pablo *et al.*, 2000 (N = 148) (30) for DQB1 only.

- Venezuela:

For HLA class I, we only found datasets from the ethnic groups Yucpa and Bari: Layrisse *et al.*, 2001 (N = 73) (32) and Layrisse *et al.*, 2006 (N = 55, available in the AFNDB only), respectively. In the first dataset, the authors were not able to differentiate the alleles C*03:02 and C*03:04. We assigned this frequency to C*03:04 only, to match with the information in second dataset for the same allele. Worth mentioning, as both studies were done on ethnic groups, they may not be representative of the country's diversity. For HLA class II, we only used the study of Layrisse *et al.*, 2001 (N = 73) mentioned before. And we did not use the dataset of Layrisse, 2006 (N = 96, available in the AFNDB) for DRB1, because this study characterized most HLAs just at 2-digit resolution and only two alleles at 4-digit resolution.

- Uruguay, Guyana, French Guiana, and Suriname: No reports in the AFNDB.

1.2 Updated Scenario, adding datasets from the literature review:

A literature review was performed to collect additional datasets from scientific articles for the Updated Scenario. We used the following search command in PubMed:

("HLA-A Antigens"[MeSH Terms] OR "HLA-B Antigens"[MeSH Terms] OR "HLA-C Antigens"[MeSH Terms] OR "HLA-DP Antigens"[MeSH Terms] OR "HLA-DQ Antigens"[MeSH Terms] OR "HLA-DRB1 Chains"[MeSH Terms] OR "HLA Antigens"[MeSH Terms] OR "HLA"[All Fields]) AND ("1990/01/01"[Date - Publication] : "2020/04/10"[Date - Publication]) AND ("Peru" OR "Bolivia" OR "Argentina" OR "Uruguay" OR "Brazil" OR "Chile" OR "Ecuador" OR "Paraguay" OR "Venezuela" OR "Colombia" OR "Suriname" OR "Guyana" OR "French Guiana" OR "Amerindian")

This command can be used directly in PubMed's website. However, we used the python script `search_pubmed_entrez` (33), which produces a table with the articles information organized in columns. The results were manually verified.

Then, datasets were selected following our inclusion criteria (see Figure 1). Some of the articles collected (11,13,15,34–49) investigated correlation of HLA alleles with certain diseases. Therefore, as they found risk/protective alleles in the study group, we decided to use the data of the control group only.

The procedure below describes how the datasets collected by country were integrated together with the datasets already selected for the current scenario. This is summarized in Table S3.

- Argentina:

For HLA class I, we only considered the study of Hurley *et al.*, 2017 (N = 1472 for A, B and C, typified by PCR-SBT) (50) due to its technological (22,23) and numerical differences versus the other eligible datasets described in the current scenario: Fernández-Viña *et al.*, 1997 (PCR-SSOP) (1) and Marcos *et al.*, 2000 (PCR-SSOP). For HLA-II, we are including the studies of Motta *et al.*, 2014 (N = 119, DQB1) (45), Fainboim *et al.*, 1994 (N = 103, DQB1) (43) and Pando *et al.*, 1999 (DQA1, DQB1 and DRB1) (51). In this last article, frequencies were not shown for all the alleles typified. However, we found the complete dataset in the first author's doctoral thesis (44).

- Bolivia:

For HLA-II, we are adding a dataset reported by Cervantes *et al.*, 2003 (N = 105) (46) for DQB1 and DRB1. As we found no studies for HLA-I with 4-digit resolution, we are including the 2-digit resolution data of Cervantes *et al.*, 2003 in Tables S4 and S5, just for illustrative purposes. These values were not used in any further analysis.

- Brazil:

For HLA class I, we are only using the study of Halagan *et al.*, 2018 (N = 4.18M for A and B, N = 92,569 for C, PCR-SBT) (52) and not the datasets of Donadi 2002 (available in the AFNDB), Nunes *et al.*, 2016 (6), Braun-Prado *et al.*, 2000 (53), Fabreti-Olivera *et al.*, 2014

(54), Castro *et al.*, 2019 (55) and Werneck *et al.*, 2016 (34), due to notorious differences in sample size and technology (22,23).

For HLA-II DPA1 and DPB1, we are only using the studies of Castro *et al.*, 2019 (N = 108 for DPA1 and DPB1, PCR-SBT) (55) and Werneck *et al.*, 2016 (N = 133 for DPB1, PCR-SBT) (34). For DQA1, we are including the datasets of Franco-Brochado *et al.*, 2016 (N = 1312, PCR-SSOP) (47), Cardozo *et al.*, 2014 (N = 173, PCR-SSOP) (48), Castro *et al.*, 2019 (N = 108, PCR-SBT) (55), and Sotomaior *et al.*, 1998 (N = 108, PCR-SSOP) (56). Sotomaior *et al.*, 1998 (56) were not able to differentiate DQA1*01:01 and DQA1*01:04, reporting a single frequency value for both alleles. We assigned this value to DQA1*01:01 due to its high abundance in the other studies considered. We did not include the study of Shimokawa *et al.*, 2016 (N = 103, PCR-SSP) (49), because the genotypification technique used has lower resolution. We did not consider the study of Reis *et al.*, 2018 (N = 641 for DQA1 and DQB1, PCR-SSOP) (57) since it reports the same control group (although in less detail) of the study of Castillo Lima Vendramini *et al.*, 2020 (already included in the current scenario).

For DQB1 and DRB1, we only used the dataset of Halagan *et al.*, 2018 (N = 193,053 for DQB1, N = 4.18M for DRB1, PCR-SBT) (52). Due to clear differences in sample size and technology (22,23), we did not consider the studies neither the studies in the current scenario, nor the studies of Cangussu *et al.*, 2011 (N = 103, PCR-SSP) (58), da Costa Lima Caniatti *et al.*, 2017 (N = 143, PCR-SSOP) (59), Donadi *et al.*, 2000 (N = 119, PCR-SSOP) (60), Fabreti-Oliveira *et al.*, 2014 (N = 551, PCR-SSOP) (54), Fernandes *et al.*, 2002 (N = 181, PCR-SSOP) (61), Freitas *et al.*, 2004 (N = 166, PCR-SSP) (62), Braun-Prado *et al.*, 2018 (N = 149 to N = 158, PCR-SSOP) (53), Gil *et al.*, 2017 (N = 297, PCR-SSOP) (63), Louzada-Junior *et al.*, 2008 (N = 156, PCR-SSOP) (64), Souza de Lima *et al.*, 2016 (N = 101, PCR-SBT) (65), Usnayo *et al.*, 2011 (N = 215, PCR-SSOP) (66), and Kay *et al.*, 2019 (N = 215, PCR-SBT) (67) and Maciel *et al.*, 2001 (N = 166, PCR-SSP) (68).

- Chile:

In addition to the datasets mentioned in the current scenario, we found three studies meeting our inclusion criteria: Castro-Santos *et al.*, 2020 (N = 160 for HLA-I A, B, C and N = 510 for HLA II DRB1) (69), Rey *et al.*, 2013 (N = 104 for HLA-I A and B, HLA-II DQB1 and DRB1) (70), and Perez-Bravo *et al.*, 1995 (N = 74, for HLA-II DQA1 and DQB1) (35). For genes DQA1 and DQB1, we did not include the articles of Díaz *et al.*, 2003 (N = 125) (71) and Santos *et al.*, 2000 (N = 255) (72) because these studies were just focused on detecting the presence/absence of few specific alleles.

- Colombia:

For HLA-II, by applying the auxiliary rule for DPB1, we are including two additional datasets, each of N = 50, reported by Briceno *et al.*, 1996 (18). For DQB1 and DRB1, we are adding the study of Del Río-Ospina *et al.*, 2019 (N = 274) (73).

- Ecuador:

No additional dataset was found for HLA-I. We applied the auxiliary rule for HLA-II, adding the study of Begovich *et al.*, 2001 (N = 83, Cayapa) for DPA1 (26). Additionally, for DQA1 and DQB1 we are including the datasets reported by De Angelis *et al.*, 2011 (N = 79) (36) and Iorio *et al.*, 2014 (N = 52) (74).

- Paraguay:

The only study that met our selection criteria is Benitez *et al.*, 2011 (N = 40, for HLA-I A, B and HLA-II DRB1) (75).

- Peru:

For HLA-I, we included the study of Olvera *et al.*, 2015 (N = 468, Lima) (37), which screened alleles of HLA-I A, B and C in 246 HIV-positive and 222 HIV-negative individuals by PCR-SBT. They found statistically significant differences in the frequency of 4 alleles, for which we used the frequencies of the control group: 9.86% for B*40:02, 1.76% for B*35:43, 1.76% for A*23:01 and 0% for B*57:03. We did not include the dataset of Arnaiz-Villena *et al.*, 2009 (N = 105) (29) for HLA-I due to technological discrepancy (22,23).

- Uruguay:

For HLA-I, we have not found datasets with 4-digit resolution. We are showing the largest study with 2-digit resolution, Alvarez *et al.*, 2006 (N = 959), in Tables S4 and S5 for illustrative purposes only (76). These values were not used in any further analysis.

For HLA-II, we only obtained the dataset of Mimbacas *et al.*, 2003 (38), reporting the allelic frequencies of DQB1 in 80 control patients.

- Venezuela:

For genes DPA1, DPB1, DQA1 and DQB1, by applying the auxiliary rule, we are including the datasets reported by Balducci-Silano *et al.*, 1995 (N = 147 for DPA1 and DPB1) (39), Rivera-Pirela *et al.*, 2016 (N = 48 for DPA1 and DPB1) (77) and Gendzekhadze *et al.*, 2004 (N = 44 for DPB1) (78), Makhatadze *et al.*, 1997 (N = 164 for DQA1 and N = 165 for DQB1) (79), Dao *et al.*, 2005 (N = 79 for DQB1) (42) and Sáenz-Cantele *et al.*, 2007 (N = 101 for DQB1) (40) in addition to the dataset of Layrisse *et al.*, 2001 (N = 73) (32), already considered in the current scenario. We are assigning the frequency reported by Sáenz-Cantele *et al.*, 2007 for DQB1*02 to DQB1*02:01, since is it the only variant of DQB1*02 reported in the other datasets for this country.

For HLA-II DRB1, it was not necessary to apply the auxiliary rule. We are only considering the datasets of Makhatadze *et al.*, 1997 (N = 160) (79), Sáenz-Cantele *et al.*, 2007 (N = 101) (40) and Fortes *et al.*, 2007 (N = 111) (41).

- Guyana, French Guiana, and Suriname: No eligible datasets were found.

1.3 Weighted Allele Frequencies by country:

WAFs by country were calculated for both the current and updated scenarios as described in the Methods section, using the data considered in each scenario as described above (see Table 3). However, not all the datasets selected by country reported identical set of alleles. A small number of alleles had frequencies reported in just some but not all the studies, which could be either an actual reflection of the population studied or caused by study particularities (small sample size not representative enough of the total population, study on ethnic or isolated groups, among other possibilities). In these cases, the weighted average calculation considers the value of zero for allele frequencies not reported in a study. This caused some weighted average frequencies to drop below the 5% cut-off. Therefore, as we are uncertain if this WAF values are trustworthy, we are also reporting the WAF values calculated ignoring the missing values. These are shown enclosed in brackets in Tables S5 and S6.

Additionally, few datasets were not entirely characterized at 4-digit resolution, reporting the frequencies of some alleles with 2-digit resolution only. For those alleles affected, we calculated the WAF using only the information available at 4-digit resolution. Therefore, in these cases we have alleles with lower sample sizes than others of the same gene in the same country. These numbers are shown enclosed in curly brackets in Tables S5 and S6.

2. References:

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