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Balancing selection and heterogeneity across the classical human leukocyte antigen loci: a meta-analytic review of 497 population studies

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Abstract

This paper presents a meta-analysis of high-resolution human leukocyte antigen (HLA) allele frequency data describing 497 population samples. Most of the datasets were compiled from studies published in eight journals from 1990 to 2007; additional datasets came from the International Histocompatibility Workshops and from the AlleleFrequencies.net database. In all, these data represent approximately 66,800 individuals from throughout the world, providing an opportunity to observe trends that may not have been evident at the time the data were originally analyzed, especially with regard to the relative importance of balancing selection among the HLA loci. Population genetic measures of allele frequency distributions were summarized across populations by locus and geographic region. A role for balancing selection maintaining much of HLA variation was confirmed. Further, the breadth of this meta-analysis allowed the ranking of the HLA loci, with DQA1 and HLA-C showing strongest balancing selection and DPB1 being compatible with neutrality. Comparisons of the allelic spectra reported by studies since 1990 suggest that most of the HLA alleles identified since 2000 are very-low-frequency alleles. The literature-based allele-count data, as well as maps summarizing the geographic distributions for each allele, are available online.

Introduction

The human major histocompatibility complex (MHC) contains over 200 genes in a 4 Mb region of chromosome 6. Approximately 40% of these genes have immunological functions, most notably the genes that encode the human leukocyte antigen (HLA) proteins. The HLA proteins are cell-surface antigens that present peptides to T-cell receptors, distinguishing self from non-self peptides. Additionally, some of them serve as ligands for killer-cell immunoglobulin-like receptors on natural killer cells and some T-cells. Extensive allele and haplotype diversity has

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been observed for the classical class I (HLA-A, -C, and -B) and class II (HLA-DRB1, -DQA1, - DQB1, -DPA1, and -DPB1) genes. Many hundreds of class I and DRB1 alleles have been observed globally and scores of alleles, many with relatively high frequencies, exist within any given population, making them the most polymorphic loci in the human genome. Specific polymorphisms at these loci have been associated with susceptibility to and protection from various auto-immune and infectious diseases, as well as certain cancers [1].

Because of their conspicuously high allelic diversity, HLA genes have been used for population studies, to study human demography, and to demonstrate trans-species polymorphism and balancing selection (the maintenance of novel and low frequency alleles at frequencies more evenly distributed than expected under models of neutral evolution). Population-level studies of HLA allelic diversity have provided insight into the selective forces that have acted to generate and maintain polymorphism in the human species [2,3]. Historical and evolutionary relationships among modern human populations have been inferred from comparisons of HLA allele and haplotype frequency distributions [4–7]. Further, variation in the allelic diversity between populations, as well as comparisons of linkage disequilibrium (LD) patterns across the HLA region, have been used to infer demographic events such as bottlenecks and founder events [3,8]. Finally, differences in allele and haplotype frequencies between populations belonging to different ethnic groups have been used to better understand associations between HLA and disease, in some cases illuminating mechanisms of disease progression and resistance [9,10] and in other cases identifying the actual disease-predisposing locus due to high LD [11,12].

Here, we present meta-analyses of allele frequency distribution data for the classical HLA loci in 497 population samples, representing 66,800 individuals in studies published over the last 17.5 years, describing measures of diversity and selection for each population at each typed locus in an attempt to summarize broad global patterns of allelic differentiation. These data and associated analyses are available in electronic form from http://www.pypop.org/popdata/.

Subjects and methods

Datasets

The data analyzed here were derived from three distinct sources (described below). Combined, these datasets constitute a collection of 497 globally well-distributed population samples, of at least 20 individuals each, representing allele frequency data for approximately 66,800 individuals in total. The 497 population samples were carefully screened for duplications (i.e., the same individuals represented in two datasets), but some populations are represented by more than one sample (e.g., at the HLA-B locus, there are five different samples of the Japanese population.)

Each population data file was annotated with a three-letter abbreviation assigning it to one of the 10 world regions shown in Figure 1 [3,13]: Sub-Saharan Africa (SSA), North Africa (NAF), Europe (EUR), Southwest Asia (SWA), Southeast Asia (SEA), Oceania (OCE), Australia (AUS), Northeast Asia (NEA), North America (NAM), South America (SAM) . These regional assignments were based on the origin of the population, in effect ignoring the last 1000 years of known human migration (e.g., people of European descent in the United States are assigned to the region EUR). Significantly admixed populations (those suspected to have origins in more than one of the 10 regions) were placed in a separate regional category: other (OTH). Each data file also includes the latitude and longitude of the population sample, inferred as accurately as possible from the information provided in the publication. The geographical coordinates of the sampling thus may not lie within the regional assignment.

Literature datasets

Datasets of HLA allele counts or frequencies were collected from a systematic review of the literature. For each of the following eight journals, every issue between January 1990 and August 2007 was surveyed for published allele frequency data: American Journal of Human Genetics, American Journal of Physical Anthropology, Human Immunology, Human Genetics, Immunogenetics, European Journal of Immunogenetics (later titled International Journal of Immunogenetics), Tissue Antigens, and Human Biology. In each issue, we identified articles describing allelic (as opposed to phenotypic) frequency data of a clearly defined population or subpopulation for one or more of the following classical HLA loci: A, C, B, DRB1, DQA1, DQB1, DPA1, and DPB1. Many of the datasets were taken from studies with an explicit anthropological focus, but control groups from case-control disease studies were also used, if the population samples were randomly selected. Nearly half of the datasets were found in Tissue Antigens. Four studies from other journals were brought to our attention and were also included.

For each article, allele frequency data were entered into a spreadsheet by hand or, when possible, copied and pasted directly from tables available via the online version of the journal article. Genotype and haplotype data (available in very few of the publications) were collapsed to allele-count data. A dual entry procedure was implemented for quality control purposes using different data entry personnel. If included in the publication, the reported allele counts were used, but more commonly, allele counts were calculated by multiplying the reported allele frequencies by the number of chromosomes ($2n$). If the sum of the allele frequencies did not equal 1, the data were rechecked against the original publication. In cases where erroneous frequencies were present in the original publication, obvious typographical errors were corrected, but in cases where the source of the error was not clear, the data were excluded from analysis. The allele-count data were then saved as flat, tab-delineated data files (described below). Fields describing the ethnicity of the population and bibliographic citation information were included in the data files. The year of publication was used as a proxy for the actual typing date of the population sample.

Publications were excluded from the literature datasets for the following reasons: more than 5% of the data were low resolution (i.e., typed at the two-digit “serological” level) or missing (e.g., “blank” alleles); the $2n$ sample size was less than 40 chromosomes; or the published data were available as part of the International Histocompatibility Workshops (IHW, described below).

The literature datasets describe 292 populations, or 35,063 individuals, with an average of 2.1 loci typed per population, and were obtained from a total of 185 publications [14–198]. The data files are available for download at http://www.pypop.org/popdata/.

International Histocompatibility Workshop datasets

Data from the 13th IHW Anthropology / Human Genetic Diversity component [199] and the 12th IHW Anthropology component [200] were also included in these analyses. Duplications between the workshop datasets and the literature datasets were carefully screened. Because they adhere to the same typing and reporting standards, the workshop datasets were used in preference to corresponding literature datasets in cases of duplication. Eight workshop population samples with a $2n$ size of less than 40 chromosomes were removed.

The final workshop datasets used for the present study describe 135 population samples, representing 17,480 individuals, with an average of 3.7 loci typed per population. Data from the 13th IHW are available from the dbMHC Web site (http://www.ncbi.nlm.nih.gov/mhc/).

Data from the 12th and 13th IHW are available from the Gene[VA] Web site (http://geneva.unige.ch/IHWdata/).

Allelefrequencies.net datasets

To augment data obtained from the literature and the IHW, HLA data from the AlleleFrequencies.net database were downloaded on 9 December 2004 from http://www.allelefrequencies.net/. This public database contains researcher-submitted allele frequency data for HLA and other loci [201]. The data were published as printed tables in the 10 September 2004 issue of Human Immunology. In cases of duplication with population data in the literature or workshop datasets, those obtained from the AlleleFrequencies.net database were excluded. The same exclusion criteria described above for the literature datasets were also applied.

The AlleleFrequencies.net datasets that were selected for the present study describe 70 populations, representing 14,287 individuals, with an average of 2.1 loci typed per population. A list of these populations, with links to the AlleleFrequencies.net database, may be accessed at http://www.pypop.org/popdata/.

Analysis

The PyPop population genetics software package

PyPop is an open-source software package designed to perform large-scale population genetic analyses on single-locus allele-count and multi-locus genotype data [202–205]. PyPop performs haplotype frequency estimation, tests for deviation from Hardy-Weinberg (H–W) equilibrium, and tests for balancing or directional selection, and computes the strength and significance of LD. The methods employed are described in [206,207]. Although originally developed to analyze the highly polymorphic HLA region, PyPop has applicability to any multi-locus genetic data. PyPop was the primary analysis platform of the Anthropology component of the 13th and 14th International Histocompatibility Workshops [5,13,199,204–210]. The PyPop input file format is an easily-parsed, tab-delimited plain-text file, and can accommodate both population allele-count data and individual genotype data.

The large number of alleles, along with the complexities of HLA nomenclature, demands certain pre-processing steps, especially for comparisons across different studies. PyPop has the ability to validate allele names by comparing them to an authoritative source, as defined by the user. For the HLA alleles examined in this study, allele names were checked against release 2.18 of the IMGT/HLA database [211,212], downloaded on 29 Sept 2007 as MSF-formatted sequence alignment files from ftp://ftp.ebi.ac.uk/pub/databases/imgt/mhc/hla/. PyPop alerts the user to unrecognized allele names, which helps to catch data entry errors.

Pre-processing is also important when dealing with the nomenclature variation present across 17 years of published studies. Some HLA alleles are only detectable using a specific high-resolution genotyping method (e.g., sequence-based typing) and would be reported under a different four-digit name using lower-resolution methods [13,209]. Other allele names have been changed or deleted entirely from the list of officially recognized alleles (see http://www.anthonynolan.com/HIG/lists/delnames.html). To achieve a common denominator of typing resolution, class I alleles are considered the same if their peptide sequences are identical across exons 2 and 3, whereas class II alleles are considered the same if they are identical across exon 2 [213]. For this study, all of the above nomenclature changes were encoded as a set of “binning rules” that PyPop applies before beginning population genetic analysis. This facilitates valid comparisons across datasets genotyped with different methods. These binning rules are available as part of the PyPop (version 0.7.0) package, downloadable at http://www.pypop.org/.

Ewens-Watterson homozygosity test of neutrality

The Ewens-Watterson (EW) homozygosity test of neutrality [214,215] provides a method to detect the effect of selection using allele frequency data. Balancing selection maintains a number of alleles at relatively even frequencies, whereas directional selection favors one or a few alleles. The EW test uses the observed homozygosity statistic (F_{obs} , defined as the sum of the squared allele frequencies) and compares this with F_{exp} , the homozygosity expected under neutral evolution (random neutral mutations and genetic drift), for a given sample size ($2n$) and number of alleles (k), as described by Ewens [214].

When the null hypothesis of neutral evolution is rejected, this test suggests the effect of either balancing selection (when $F_{obs} \ll F_{exp}$) or directional selection (when $F_{obs} \gg F_{exp}$). An extreme demographic event in the history of the population (e.g., a founder effect or population bottleneck) may also increase F_{obs} relative to F_{exp}. Although it is possible to perform a one-sided test against the alternative hypothesis of balancing selection or directional selection (many software packages do report a one-sided test), here we report p-values for a two-sided test, which results in a more conservative test for loci at which balancing selection is suspected. The p-values are based on Slatkin's [216,217] implementation of a Monte-Carlo approximation to the EW homozygosity test of neutrality. It is also worth noting that while F_{obs} is calculated under the H–W assumptions, the EW test is not a test of H–W proportions.

The degree of deviation between F_{obs} and F_{exp} is described by the normalized deviate of homozygosity (F_{nd}), defined by Salamon and coworkers [218] as $F_{\mathrm{nd}} = \left(F_{\mathrm{obs}} - F_{\mathrm{exp}}\right) / \sqrt{\mathrm{Var}(F_{\mathrm{exp}})}$. This statistic permits comparisons between population samples that have different numbers of alleles and sample sizes, such as those in the present study. Balancing selection results in negative F_{nd} values whereas directional selection, along with certain demographic events, leads to positive values.

For meta-analysis, the mean F_{nd} for groups of populations were tested using the t-test and the sign test. A two-tailed t-test can be used to test the null hypothesis that $\overline{F_{\mathrm{nd}}}$, averaged over m different populations, is significantly different from zero [218], because under the null hypothesis of neutral evolution, $\overline{F_{\mathrm{nd}}}$ is approximately normally distributed with a mean of zero and a variance of $1/m$. Rejection of the null hypothesis suggests the effect of balancing selection ($\overline{F_{\mathrm{nd}}} \ll 0$), directional selection ($\overline{F_{\mathrm{nd}}} \gg 0$), or demographic events in the populations' histories. In this latter case, selection can sometimes be distinguished from demographic effects by comparison of $\overline{F_{\mathrm{nd}}}$ values (or individual F_{nd} values for a single population) at multiple loci, with the assumption that evidence for selection will be strongest at a specific locus, while a demographic effect should be evident at all loci. The sign test uses the expectation of equal proportions of negative and positive F_{nd} values, for a collection of populations, under neutral evolution. The sign test can be used to test the null hypothesis of equal proportions for the two categories [219].

Year of initial identification of HLA alleles

When available, the earliest year of publication of the article(s) describing each allele in the corresponding reference page on the Anthony Nolan Trust HLA Informatics Group Web site (http://www.anthonynolan.com/HIG/seq/refs/) or the year of creation of the record for each allele in the EMBL-EBI IMGT/HLA database (http://www.ebi.ac.uk/imgt/hla/) was used to represent the year in which that allele was first identified. After the truncation of allele names to four digits, the earliest such year was taken as the year of initial identification of that particular peptide sequence.

Genetic differentiation within and between regions

To compare the degree of genetic differentiation within and between different global regions, we used PHYLIP v3.6 [220] to calculate Nei's Standard Genetic Distances between all pairs of populations at the HLA-A, -C, -B, -DRB1, and -DPB1 loci. We calculated the overall mean genetic distance for the populations at each locus, the mean genetic distance for each region (and certain subregions) at each locus. Infinite genetic distances were ignored for these calculations. Finally, each regional or subregional mean genetic distance value was divided by the overall mean genetic distance at each locus, generating the regional fraction of the overall genetic distance seen in each locus. Considered relative to one another, these fractions indicate the degree of differentiation in allele frequency distributions for the populations in each region and subregion.

Because data are available for different sets of populations at each locus, we restricted these calculations, such that we used only those populations common to individual pairs of loci, and only those pairs of loci with enough populations to compare (i.e., intraclass I comparisons, class I - DRB1 comparisons, and the DRB1 vs. DPB1 comparison).

Mapping and geographic allele frequency interpolation

Maps were plotted using the Generic Mapping Tools (GMT) package [221], of which the blockmean and surface functions were used to interpolate a two-dimensional allele frequency distribution from the available point estimates. GMT mapping scripts are available for download at http://www.pypop.org/popdata/.

Results

Number of Population Samples

Table 1 summarizes the number of population samples (*m*) of the three meta-datasets, describing coverage by locus, by world region, and over all regions. The population samples are illustrated geographically in Figure 2, in which each population is plotted according to its sampling location (not necessarily the same as its regional assignment). Global representation of published HLA data is biased towards EUR and East Asia (SEA+NEA), with especially poor representation of Africa (SSA+NAF), SWA, and AUS; 128 East Asian and 117 EUR populations (representing approximately 18,400 and 24,700 sampled individuals, respectively) are included in the combined dataset, whereas only 55 African and four AUS populations (6,000 and 412 individuals, respectively) are included. The sampling bias is most pronounced for class II HLA loci, which were the first loci to be typed extensively and at high resolution; the earliest HLA molecular typing studies tended to sample EUR and East Asian populations, and populations from these regions represent 53% of the populations (and 68% of the individuals) with class II frequency data. In contrast, EUR and East Asian populations represent only 42% of the populations (and 58% of the individuals) with class I frequency data. Of the loci included in these analyses, DRB1 is best represented, with frequency data available for 259 populations (representing approximately 40,700 individuals), while the DPA1 locus is the least well-represented locus, with only 45 populations (3,800 individuals).

In total, there are 416 population samples with class II HLA data and 171 population samples with class I HLA data. Whereas data for fewer population samples and sampled individuals are available for the class I loci, more populations have data across multiple class I loci than across multiple class II loci; the mean number of class I loci typed per population with class I data is 2.43, whereas the mean number of class II loci typed per population with class II data is 2.03. Thus, although there are fewer class I data overall, interlocus comparisons are more likely to pertain to the same population samples for class I than for class II.

Number of distinct alleles (*k*)

The number of distinct four-digit alleles was counted for each population and locus. The mean number of alleles ($\bar{k}$) is shown in Table 1, tabulated by locus, by world region, and over all regions. The distribution of *k* in each region is shown graphically in Figure 3. In general, the geographic regions SSA, NAF, EUR, SWA, and NEA have the highest values of *k* across all HLA loci compared to other world regions. However, the non-geographic grouping OTH, which includes populations that are significantly admixed, with ancestry deriving from two or more geographic regions, often has even more alleles, as expected; this is especially prominent at HLA-B and -DRB1. Compared with the other loci, DQA1 and DQB1 have the smallest variance in *k*, while HLA-B has the highest variance.

Of course, the number of alleles detected in a given population (*k*) strongly depends upon its sample size (2*n*). However, this meta-analysis was restricted to sample sizes of $2n \geq 40$ chromosomes. Furthermore, the overall mean sample size for the datasets presented here was 256 chromosomes, and minimum regional mean (for OCE) was 128 chromosomes. At this sampling level, many loci do not exhibit any *k* versus 2*n* dependency. However, the highly polymorphic loci HLA-B and -DRB1 do exhibit a slight relationship. This may bias the $\bar{k}$ estimate for OCE at these loci.

Number of alleles versus year of publication

We also examined the relationship between *k*, the year of initial identification of each allele, and the year of publication of each dataset. We combined recent (i.e., since 2002) population samples from within selected regions (EUR, SEA, and Africa [SSA+NAF]) in order to estimate regional allele frequencies and ranked these regional frequencies by the year in which each identified allele was first described. Within each of these regions, approximately 95% of regionally prevalent (i.e., allele frequency > 0.02) alleles had already been described by 1990 for class II and by 1995 for class I, with an average of 99.7% of the reported alleles falling into the “Common and Well Documented” (CWD) allele category of Cano et al. [213] (details are available at http://www.pypop.org/popdata/). Given the dramatic increases in the numbers of novel alleles that have been identified in the last seven years, it might be expected that datasets published in the 1990s would be deficient in terms of the number of distinct alleles identified when compared with more recently published datasets, potentially confounding meaningful comparative analyses. However, when values of *k* in datasets published in the 1990s are compared with datasets published in the 2000s, and when alleles identified in each group of datasets are assigned to CWD or non-CWD categories, it becomes clear that the overwhelming majority of recently reported population-level allelic diversity is consistent with that reported in the 1990s, suggesting that population samples from both time periods are comparable.

Observed homozygosity (F_{obs})

The distribution of the observed homozygosity (F_{obs}) is illustrated in Figure 4. Generally, F_{obs} is inversely proportional to *k*, as expected: the lowest F_{obs} values are found in SSA, NAF, EUR, SWA, NEA, and OTH, whereas the highest F_{obs} values are often found in NAM and SAM. The variance of F_{obs} tends to be much smaller than that of *k* (e.g., compare these two distributions for SSA at the B locus.) This is because the difference in *k* in these diverse populations is primarily due to low-frequency alleles that have little effect on F_{obs}.

Normalized deviate of homozygosity (F_{nd})

For each population, the normalized deviate of homozygosity (F_{nd}) and the corresponding two-sided *p*-value was calculated. Negative F_{nd} values result when F_{obs} has lower than expected homozygosity (F_{exp}). Significantly negative F_{nd} values imply balancing selection and/or high

levels of gene flow, whereas significantly positive values imply directional selection and/or extreme demographic effects as a result of genetic drift.

The mean F_{nd} ($\overline{F_{\mathrm{nd}}}$) values, tabulated by locus and geographic region, are illustrated in Table 1. $\overline{F_{\mathrm{nd}}}$ is negative in all geographic regions for loci A, C, B, DRB1, DQA1, and DQB1. Only DPA1 and DPB1 show positive $\overline{F_{\mathrm{nd}}}$ values in some regions; DPB1 in particular has $\overline{F_{\mathrm{nd}}}$ values very close to zero for most regions. The distribution of F_{nd} is illustrated in Figure 5. DQA1 displays the strongest evidence for balancing selection, and the least variance in F_{nd}, while the DPB1 F_{nd} distribution is compatible with neutral expectations and displays the greatest variance both within and between regions.

The percentage of populations with negative ($F_{nd} < 0$) and significantly negative ($F_{nd} \ll 0$) values of F_{nd} is summarized in Table 1 (by locus, by region, and over all regions, and including statistical significance) and illustrated in Figure 5 (by locus and region) and in Figure 6 (by locus and indicating significance across all regions and including significantly positive F_{nd} results). Loci DQA1, C, and DQB1, in that order, have the greatest percentage of populations with significantly negative F_{nd} values, whereas DPA1 and DPB1 have the lowest percentage.

The distribution of F_{nd} values may also serve as the basis for statistical tests. *p*-values for the *t*-test (based on $\overline{F_{\mathrm{nd}}}$ and the central limit theorem) and the sign test (based on the relative proportions of negative and positive F_{nd} values) are presented in Table 1 by locus and geographic region. In most cases, the *t*-test and the sign test are in fairly close agreement, across regions and overall, although the *t*-test has more statistical power. Using both tests, significantly negative $\overline{F_{\mathrm{nd}}}$ values (or F_{nd} distributions) are found at class I loci B and C and at class II loci DQA1, DQB1, and DRB1 in the majority of world regions ($p \ll 0.01$, indicated in boldface in Table 1). The other loci, A, DPA1 and DPB1, fail to demonstrate significance for most world regions. This lack of significance may be due to F_{nd} distributions that are close to the neutral expectation of zero, as is the case for A and DPB1, or it may be due to the low power of these statistical tests at loci with few population samples, as in the case for DPA1.

When all world regions are considered together, all HLA loci except DPB1 and DPA1 demonstrate highly significantly negative $\overline{F_{\mathrm{nd}}}$ values (or F_{nd} distributions) by both the *t*-test and sign test ($p < 10^{-8}$; see Table 1). DPA1 also demonstrates signs of balancing selection, despite the small number of population samples ($p < 10^{-4}$, *t*-test). DPB1, however, is strikingly compatible with neutral expectations.

Ranking the relative strengths of selection across loci

To better understand the relative strength of balancing selection (as evidenced by the F_{nd} statistic), the distribution of F_{nd} values between each pair of loci was examined with a permutation test. The resulting relative rank order of $\overline{F_{\mathrm{nd}}}$ values is DQA1 $\ll$ C < DQB1 $\ll$ DRB1 < B $\ll$ A $\ll$ DPB1, where $\ll$ indicates a significant difference between $\overline{F_{\mathrm{nd}}}$ ($p<0.01$, asymptotic 2-sample permutation test). DPA1 has a $\overline{F_{\mathrm{nd}}}$ value between that of HLA-B and A, but it is not included because the small number of populations sampled at this locus minimizes the statistical power of the permutation test.

With respect to the strength of selection evident among the class I and class II loci, the differences cannot be solely attributed to *k*, the number of alleles per locus; the B and DRB1 loci are the most polymorphic, yet they fall in the middle of the rank order of strength of selection.

Regional differences of F_{nd}

Considering the results by region, SSA, EUR, SWA, NEA, and OTH have the greatest number of loci (six) with significantly negative $\overline{F_{nd}}$ values ($p < 0.01$, *t*-test and sign test). This cannot be solely attributed to the number of population samples per region: SEA and OCE, for example, are also well-sampled regions.

NAM, on the other hand, shows a trend of $\overline{F_{nd}}$ values elevated relative to other regions, at most loci. Very few NAM populations have significantly negative F_{nd} values. The most striking example is DPA1, where NAM has a significantly *positive* F_{nd} distribution ($p \leq 0.0001$, *t*-test).

The overall ("ALL") summary for each locus was calculated by averaging across all population samples in all regions (Table 1). We also calculated averages of the regional averages, and the results were nearly identical to that observed using the overall averaging method (results not shown).

Genetic differentiation within and between regions

To compare the degree of differentiation in allele frequency distribution in areas that have been densely sampled to the degree of differentiation over an entire region, we calculated the fraction of the overall mean Nei's standard genetic distance for populations in each region for which data were available for both loci in all pairs of loci. In addition, we calculated these fractions for several densely sampled and well-defined subregions. Data for 13 aboriginal populations from Taiwan (TWN) were available for the class I and DRB1 loci; three of these populations are admixed and 10 are aboriginal; the set of all 13 populations is denoted as SEA-TWN, and the set of 10 populations is denoted as TWN. Data for eight populations from Papua New Guinea (OCE-PNG) were available for the class I loci, and data for four were available for the class I loci. These were further subdivided into PNG Highland (PNGH) and PNG Lowland (PNGL) categories.

These fractions are shown in Figure 7 for comparisons between pairs of class I loci and between class I loci and the DRB1 locus, and in Figure 8 for comparisons between the DRB1 and DPB1 loci. More than 100 populations were shared among the class I loci (135 between A and B, and 105 between both A and C and B and C), whereas fewer were shared in comparisons of the class I loci with DRB1 (79 between A and DRB1, 74 between B and DRB1, and 61 between C and DRB1), and 66 were shared between DRB1 and DPB1. Very few populations were shared in comparisons between the class I loci and the DPB1 locus (26 between A and DPB1, 20 between B and DPB1, and 18 between C and DPB1) and these comparisons are not presented. It follows that there will be little overlap in the set of populations common to the DRB1 and DPB1 loci and the sets of common populations in comparison between the various class I and DRB1 loci; because of this, the figures for these comparisons are presented separately.

The regional fraction of the overall Nei's standard genetic distance is greater than 1 in some cases (e.g., SAM at HLA-A and OCE-PNG at DRB1) as a result of the extremely large degree of differentiation between populations in these regions at these loci. Many of the values for a given region are the same or very similar for the intraclass I loci comparisons, as a result of HLA-A, -C, and -B data being available for the same population in the largest number of cases.

As has been noted previously [5,7], the degree of differentiation for SSA, NAF, and EUR populations is generally lower than that for SEA, OCE, NAM and SAM populations, especially at the class I loci. Here, we can see that the degree of differentiation in densely sampled subregions is comparable in many cases with (or even greater than) that for SSA, NAF, and EUR. In particular, the 10 non-admixed aboriginal Taiwanese populations demonstrate greater

differentiation than SSA, NAF, and EUR at the HLA-B and –C loci and greater differentiation than NAF and EUR at the DRB1 locus. At the DRB1 and HLA-C loci, TWN (which constitutes approximately half of all SEA populations in these comparisons) displays levels of differentiation that are comparable to SEA. Similar patterns are seen for the PNGH and PNGL subregions at all loci. In most instances, differentiation in PNGH is observed at levels comparable with entire regions. At the HLA-A locus, PNGH populations display greater differentiation than any region other than SAM, and at HLA-B, PNGL populations display greater differentiation than any region other than SEA.

Discussion

The large quantity and broad scope of data available in published papers are the motivation for this meta-analysis of HLA allele-count data. Although working with these data poses challenges typical of meta-analytic studies (e.g. data entry errors and problems inherent in making comparisons between studies published over 17 years), such challenges have been minimized in the current study through the combination of human error-checking of the primary data and the use of PyPop to validate and bin allele names to analytically relevant common denominators. The literature-based data compiled here are available for public download and may prove useful for future studies of anthropology and HLA diversity, transplant registry analyses, and the validation of control populations in disease studies.

The large number of populations included here provides an opportunity to compare the distributions of summary statistics of allele frequencies for populations from different regions of the world. Although some of the results here are similar to those of previous meta-analyses (discussed below), the breadth and depth of the datasets assembled for this study permit statistical tests among some genetic loci and world regions that may not have been previously possible. In terms of typing schemes, sample sizes, and perhaps quality control, there is a fair amount of heterogeneity between and among the three meta-datasets assembled for this study. However, there were no substantive differences in allelic diversity among them when compared by region and locus. Certain regions of the world (e.g., EUR and SEA) are better represented than others, which might bias the overall average summary statistics presented in Table 1. However, when the overall averages were compared with the average of regional averages, results were nearly identical.

In light of the ever-growing list of known HLA alleles (a list that continues to grow dramatically every year), the lack of correlation between *k* and dataset year is perhaps a surprising result. However, the alleles identified in recent years tend to be very-low-frequency (and even unique) alleles and so do not greatly affect the results of older studies. This, in turn, suggests that the bulk of recently detected allelic polymorphism may not significantly affect meta-analyses of HLA diversity spanning decades because the vast majority of alleles present in most populations had been described by 1995 for class I loci and by 1990 for class II loci. However, an understanding of the distribution of these low-frequency and rare alleles is still important for disease studies and for determining the chance of finding a suitable transplant donor.

The EW homozygosity test of neutrality has proven to be a useful tool for detecting selection at HLA loci [3,7,209,218,219,222–231], making it an appropriate method for these meta-analyses. This meta analysis reveals an extremely strong signal of balancing selection at DQA1, HLA-C, and DQB1. The result for HLA-C is interesting because comparative population genetic data at this locus have been scarce until recently; allele-level HLA class II typing methods were developed much earlier than those for class I, and HLA-C genotyping is still less common than -A and -B typing. Data for DPA1, the least typed of the eight classical loci, are also collected here in quantity for the first time, although there are insufficient population samples at this locus to draw conclusions with high statistical power.

It is important to keep in mind that just because the EW test does not demonstrate evidence of balancing selection (e.g., at DPB1), this does not mean selection is not operating. At the same time, the strikingly different patterns observed between different loci (e.g., DPB1 compared with other loci) cannot be explained by demographic forces alone. Further, the consistent and differing patterns between the loci argue for a major role of selection at these loci, combined, of course, with demographic effects.

The observation that evidence for balancing selection in this study is strongest at the DQA1 locus is interesting. Although the DQA1 and DQB1 loci display low levels of diversity relative to extremely polymorphic loci like DRB1, it should be noted that the diversity of DQ proteins may be comparable to that for DR proteins. The seven DQA1 alleles and 11 DQB1 alleles observed on average in each population can form potentially 77 distinct DQ proteins at the population level (although not all DQA1-DQB1 combinations will result in functional molecules). In contrast, the 22 DRB1 alleles observed on average in each population can form, at most, 44 distinct DR proteins, because there are only two unique DRA alleles to form the alpha subunit. The strong balancing selection seen at the DQA1 and DQB1 loci may reflect selection for increased diversity of DQ proteins, as opposed to individual DQA1 or DQB1 alleles. Although balancing selection is clearly at work at the DRB1 locus, this locus may be under stronger selection for allelic diversity than for protein diversity.

Locus-level comparisons with previous studies

A subset of the literature data presented here was previously analyzed by Tsai and Thomson [219]. This analysis, encompassing approximately half of the present literature dataset, provided a tantalizing picture of locus-to-locus variation and a convincing argument for the value of meta-analysis of literature data. As in the current study, the authors reported the greatest evidence for balancing selection at DQA1, followed by DQB1, DRB1, B and A, with very little evidence at DPA1 and DPB1. Sanchez-Mazas [7] also recently performed EW tests using the data from the 12th and 13th IHW. The present results are compatible with that study, in which the DPB1 locus did not exhibit any sign of balancing selection, HLA-A exhibited almost no evidence, and DQA1 exhibited the strongest evidence, followed by HLA-C (according to the percentage of populations demonstrating significant rejection). The current analysis is able to extend the results of these two analyses because of the large number of additional studies considered. As such, there is now adequate data to make useful comparisons at HLA-C and also to stratify the results by world regions.

Meyer et al. [3] examined class I loci in 20 populations and class II loci in 17 populations (all of which are included in the workshop dataset of the current study), chosen to represent a global sampling of human populations. The $\overline{F_{\mathrm{nd}}}$ values presented here are very similar at all loci except DRB1 (Meyer et al. find $\overline{F_{\mathrm{nd}}} = -0.22$, not significant, as compared to −0.70, significant [$p = 3.1*10^{-37}$, *t*-test], in the present study.) The difference is most likely due to the smaller number of populations being averaged and the greater influence of outlier populations such as East Timorese and Guarani-Nandewa in the Meyer et al. study. Although we also observe several exceptionally high DRB1 F_{nd} values among populations from OCE, NAM, and SAM, the bulk of these regional distributions lies more or less in line with other world regions, with the preponderance of populations having negative F_{nd} values (Figure 5).

Salamon et al. [218] examined three class II loci (DRB1 and DQB1 in 23 populations and DPB1 in 14 populations) using data from published literature and found the most negative $\overline{F_{\mathrm{nd}}}$ at DQB1 ($\overline{F_{\mathrm{nd}}} = -0.79$ compared to −0.88 in the present study [both results significant, $p \leq 0.0001$, *t*-test]). However, differences with the present study are again seen at DRB1 ($\overline{F_{\mathrm{nd}}} = -0.38$, not significant, compared to −0.70, significant, in the present study) and also at DPB1 ($\overline{F_{\mathrm{nd}}} = -0.27$ compared to 0.01 in the present study, although neither significantly

different from zero). Again, the differences can be explained by the small number of populations being averaged and the correspondingly large influence of outliers (such as the Javanese and Indonesian populations) in the Salamon et al. study. Mack et al. [4] concluded that the high F_{nd} values observed in these OCE outlier populations were the result of selection in response to a local pathogen. Valdes et al. [226] examined variation of class II loci, considered at the locus and amino acid level, in 22 populations from the 12th IHW, with similar results to those of the Salamon et al. study.

On a smaller scale, Hedrick and Thomson [222] examined HLA-A and -B, using serological data (i.e., two-digit allele names) in 22 populations, most of which were European or of European descent. They found 11 populations at HLA-A and 14 at HLA-B to have significantly lower homozygosity than expected under neutrality. Although the present study reported less evidence for balancing selection at HLA-A, when we reanalyzed the data at the two-digit level (results not shown), the results were closer to those of Hedrick and Thomson [222]. Indeed, most loci show more negative F_{nd} values when analyzed at the two-digit level versus the four-digit (amino acid) level.

Regional comparisons

The results presented here agree with the observation that relatively high genetic diversity (i.e., lowest F_{obs} values) is commonly found among African populations [232]. High diversity of class I loci in NEA populations was also recently described [3], but there were insufficient data to draw conclusions at class II loci. NEA populations are particularly well-represented among the literature datasets, and we observe mean F_{obs} for NEA populations similar to the low values found in SSA and EUR, especially at class II loci.

OCE populations appear to have a greater range of F_{nd} values at DRB1 than other loci and regions. This result may be due in part to the large number of OCE populations included in the literature dataset at this locus, but likely also reflects heterogeneity in the demographic histories of the islands that constitute this region, because the OCE populations included in this meta-analysis extend from Indonesia across the Pacific into Polynesia (see Figure 1). Populations in western OCE might be expected to display allele spectra similar to SEA populations, whereas Polynesian populations in eastern OCE are likely to have experienced successive founder effects over the last 1000–1500 years, as the Polynesian islands were discovered and colonized.

For individual populations, comparisons of F_{nd} results are not always in concert across different loci. For example, a Javanese population has a conspicuously high F_{nd} of +2.94 at DRB1 ($p < 0.05$, two-tailed EW test of neutrality). However, the F_{nd} value at the DPB1 locus in this same Javanese population is negative (−0.6769) and consistent with neutral expectations. Similarly, the $\overline{F_{\mathrm{nd}}}$ of NAM at DPA1 (m=5 populations) is far above the mean for the rest of the world (0.93 versus −0.72). Although NAM has among the highest $\overline{F_{\mathrm{nd}}}$ across other loci as well, the result for DPA1 are exceptionally elevated relative to the rest of the world.

It is difficult to disentangle the complex interplay of selection, demography, and genetic linkage creating these patterns. Population bottlenecks may be responsible for the elevated F_{nd} values seen at some loci in isolated populations, even while those same populations maintain a large part of their ancestral diversity at other HLA loci, presumably as a result of the influence of balancing selection, linkage disequilibrium, or a combination of these two forces. The ability of balancing selection to maintain diversity in MHC genes despite the loss of genetic diversity in other genes during a population bottleneck has been described in another mammalian species [233].

Mack and Erlich [5] and Sanchez-Mazas et al. [234] noted a high level of differentiation in the HLA-B and -C allelic frequency distributions of SEA populations, and in particular of

aboriginal Taiwanese populations (relative to other regions of the world). Mack and Erlich [5] speculated that densely sampled populations in other areas of the world might display comparable levels of differentiation. This has significance for anthropology and diversity studies, as well as applications that rely on such studies (e.g., selecting a control population for a disease association study or selecting a target population for transplant registry donor recruitment) as it challenges the assumption that a broad, diffuse sampling of populations is sufficient to obtain an adequate understanding of the global distribution of HLA polymorphism.

To test this, we calculated the mean pairwise Nei's standard genetic distances at the HLA-A, -B, -C, -DRB1, and -DPB1 loci for populations in each global region, as well as for aboriginal Taiwanese populations and populations from Papua New Guinea. These comparisons demonstrate considerable differentiation among populations from relatively small areas. The area of Taiwan is 35,801 square kilometers, and the area of Papua New Guinea is 462,840 square kilometers (although the individual Highland and Lowland regions are necessarily smaller). In comparison, Europe has an area of more than 10 million square kilometers, and Africa over 30 million. It may be the case that these island populations have been isolated from one-another for considerable time, but if the pattern of significant differentiation in populations from relatively small areas proves to be the norm around the globe, then higher density sampling methods may be required in order to more accurately assess global patterns of polymorphism distribution.

The meta-dataset presented in the current study can be used to estimate the geographic distribution for each allele. Figure 9 shows the frequency distribution of the DRB1*1501 allele, as interpolated from 225 non-migrant populations. (Additional maps for each observed HLA allele at all eight classical loci are available online at http://www.pypop.org/popdata.) These maps are valuable as first approximations of the global distributions of common alleles. However, they should not be overinterpreted; the frequency clines were generated from the primary data by an algorithm that does not take into account geographic barriers (cf., discussion by Liu et al. [235]). It is also important to note that these maps are constructed from allele frequency data, not summary measures (e.g., principal components), which are often used to map geographic trends between populations. However, as such, these maps still provide a useful allele frequency reference tool and also allow some interesting comparisons with previously described population genetic patterns.

For example, recent studies have investigated clines in allele frequencies for KIR and their HLA ligands [236,237] as well as clines in genetic diversity for non-MHC data [238,239]. Single et al. [237] observed a decreasing trend in the frequencies for HLA-B Bw4 and HLA-C C-group2 alleles with distance from Africa. These same clinal patterns are evident for some allele frequency results from the current meta-analysis (e.g., C-group1 alleles: Cw*0303, *0304, *0702, *0801; C-group2 alleles: *0501, *0602, *1701), but not for others (e.g., C-group1 alleles: *0701, *0802, *1601; C-group2 allele: *1502). Individual maps may also reveal allele-specific patterns of global diversification. For example the B*4002 allele is seen at low frequencies in SSA, NAF, and EUR, but at high frequencies in NEA, NAM and SAM.

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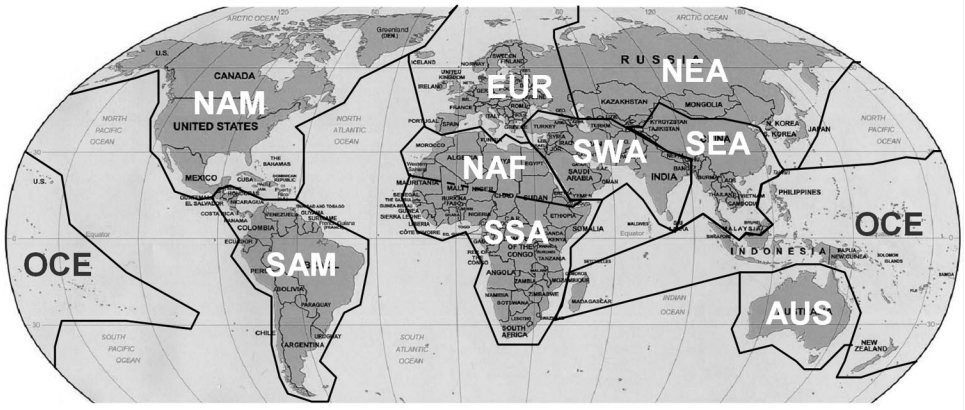

Figure 1. Geographical categories for populations

SSA = Sub-Saharan Africa; NAF = North Africa; EUR = Europe; SWA = Southwest Asia; SEA = Southeast Asia; OCE = Oceania; AUS = Australia; NEA = Northeast Asia; NAM = North America; SAM = South America. Admixed populations are assigned to the category other (OTH). The groupings are as recommended in references [3,13].

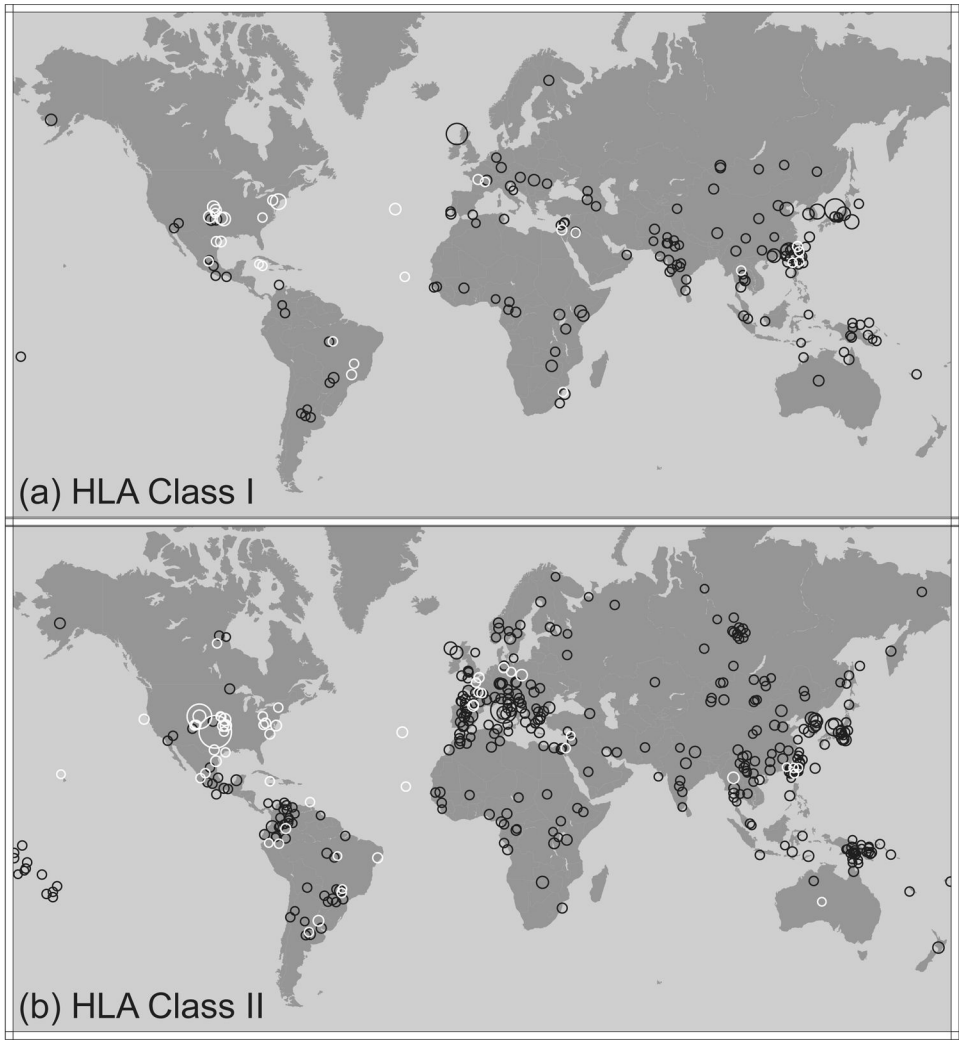

Figure 2. Population samples plotted on global map

(a) Populations with class I HLA data; (b) Populations with class II HLA data. Circle size is relative to 2N sample size. Black symbols are native populations, which are assigned to the geographic region in which they were sampled. White symbols are populations that have migrated in the last 1000 years; when considered to be admixed, these populations are assigned to the OTH category, otherwise they are assigned to their region of origin (see Subjects and methods for details).

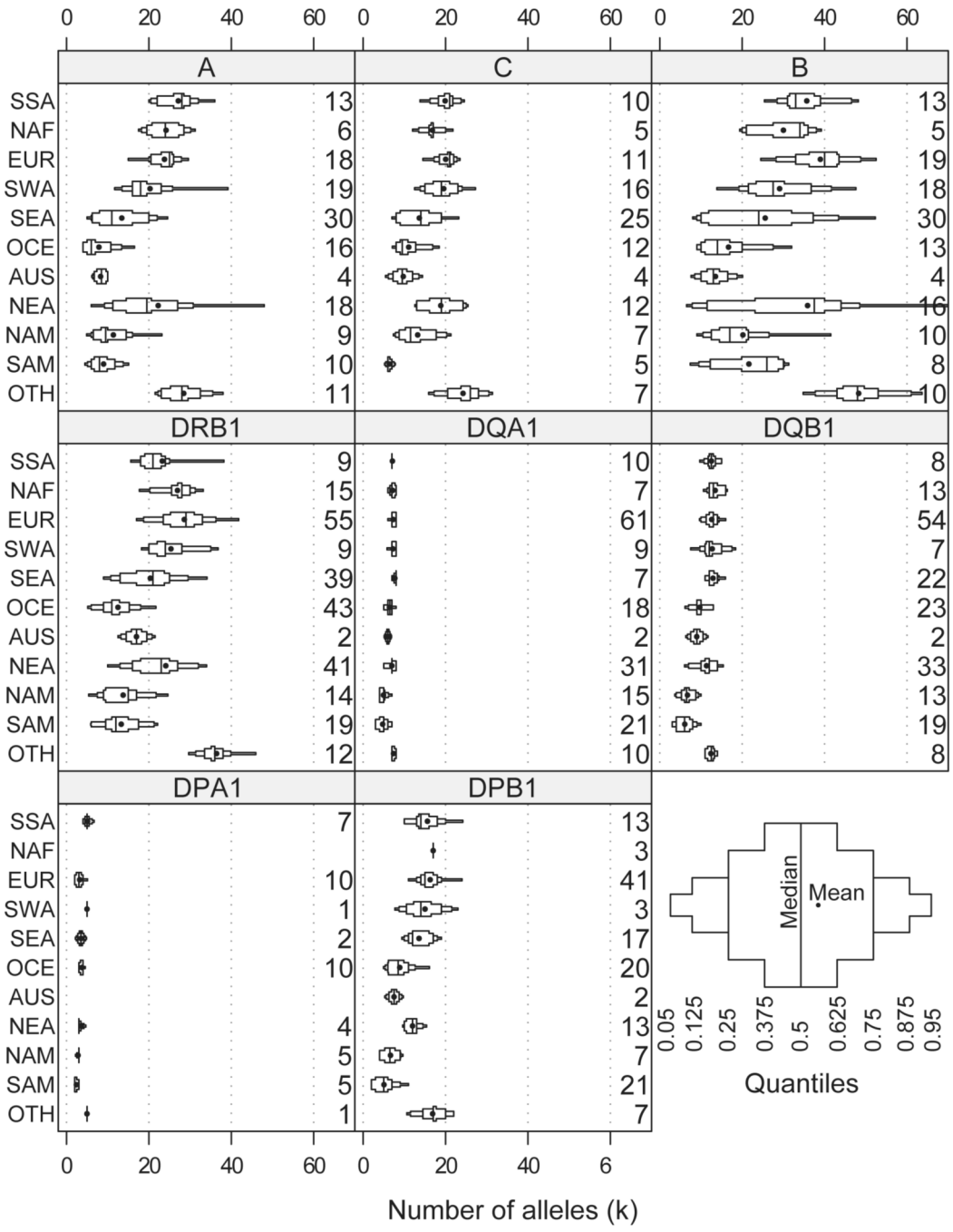

Figure 3. Modified box plot illustrating the distribution of allele number (*k*) by locus and region

The median value is represented by the middle vertical line and the mean value by the point. The number on the right of each subplot represents the number of populations for each locus and region combination. The panel in the bottom right illustrates the interpretation of quantiles.

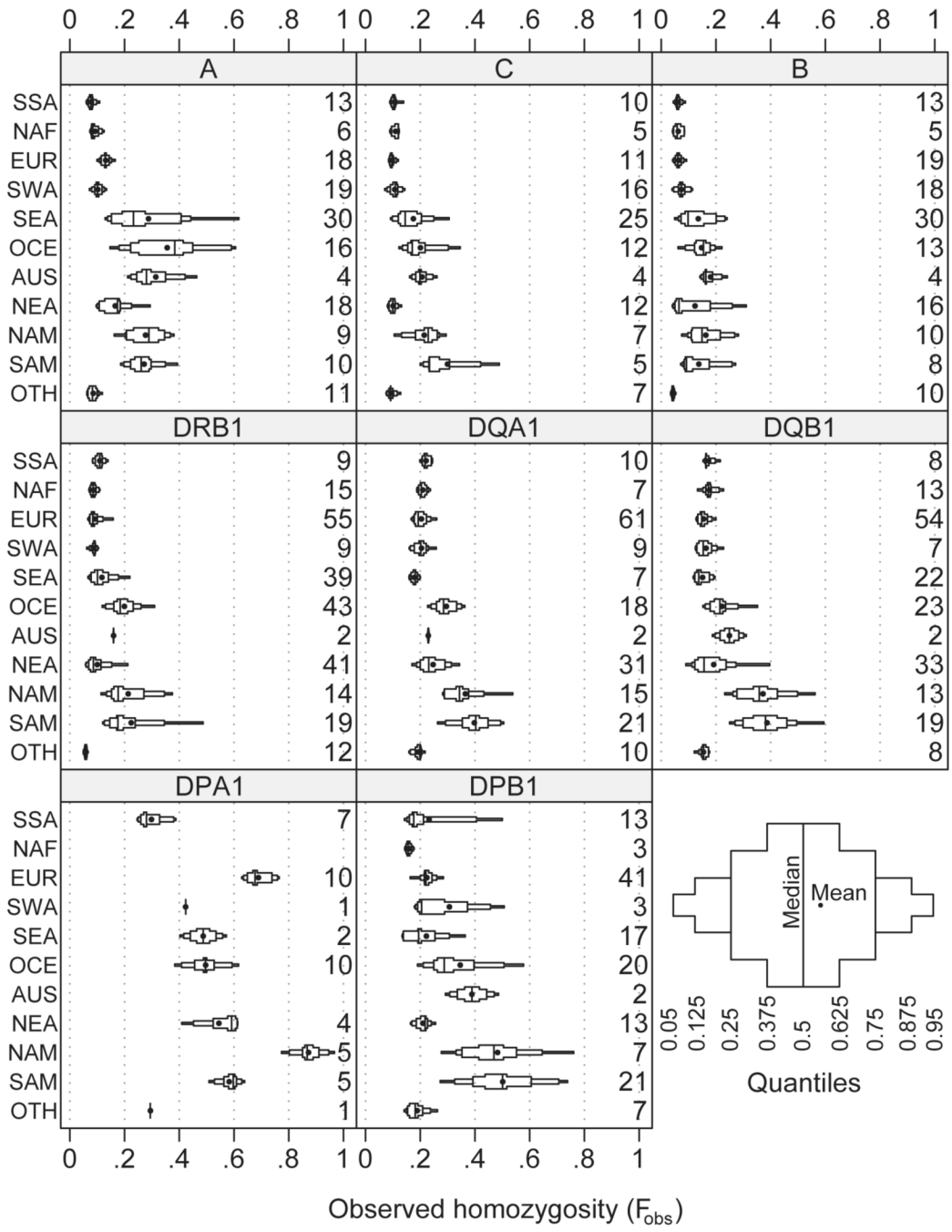

Figure 4. Modified box plot illustrating the distribution of observed homozygosity (F_{obs}) by locus and region

For an explanation of the plot elements, see the legend to Figure 3.

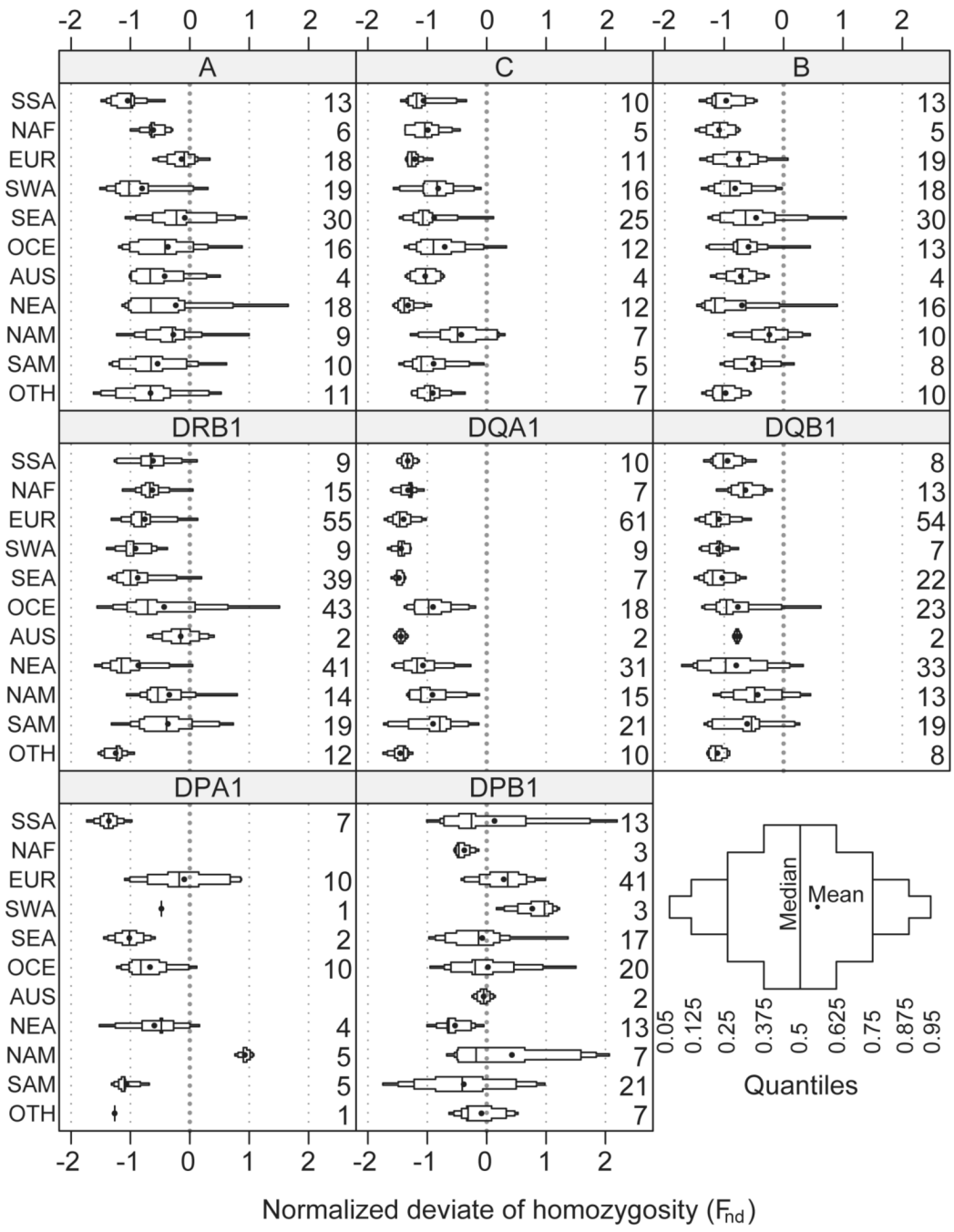

Figure 5. Modified box plot illustrating the distribution of the normalized deviate of homozygosity (F_{nd}) by locus and region

For an explanation of the plot elements, see the legend to Figure 3.

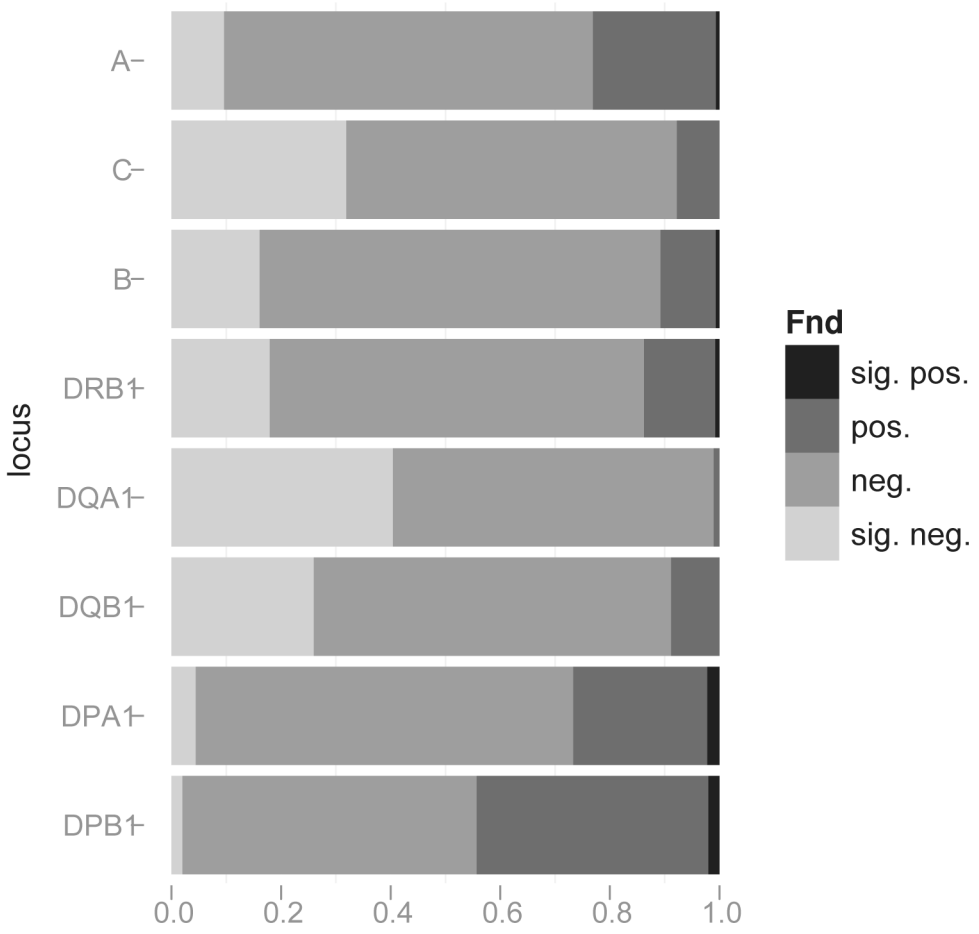

Figure 6. Bar plot of F_{nd} results

Shading indicates proportions of populations with significantly negative (suggestive of balancing selection and/or gene flow), negative, positive, and significantly positive (suggestive of directional selection and/or genetic drift) values of the normalized deviate of homozygosity (F_{nd}), as tested by Slatkin's implementation of the Monte Carlo approximation of the Ewens-Watterson exact test, using a two-tailed test ($p < 0.05$) of the null hypothesis of neutrality.

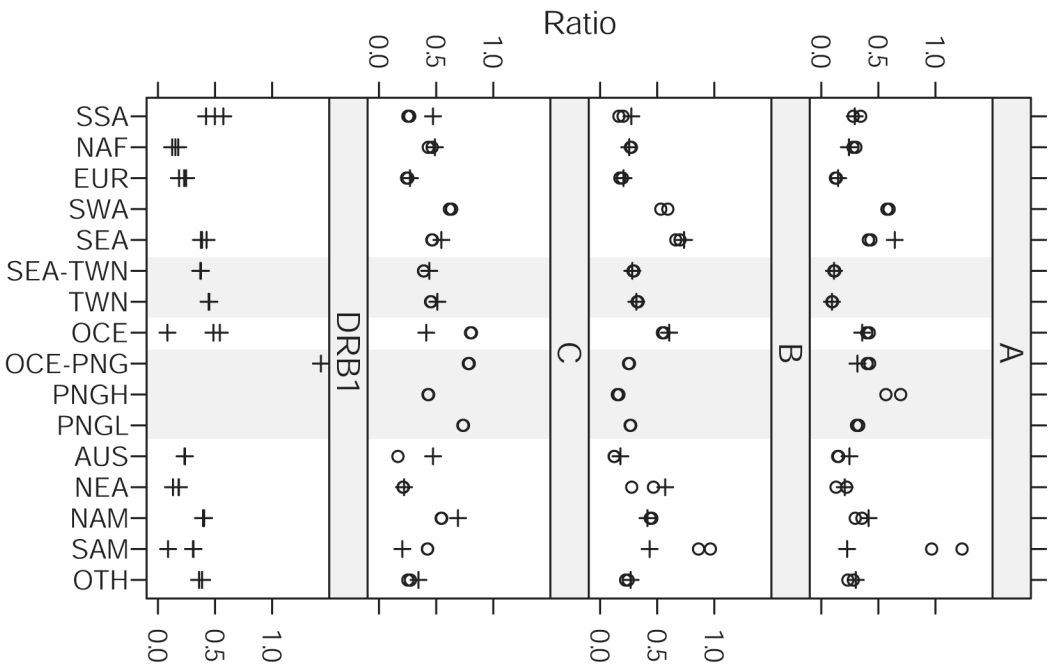

Figure 7. Genetic differentiation present in world regions and subregions

Comparisons of the same subsets of populations are illustrated with circles (intraclass I) or crosses (class I - DRB1).

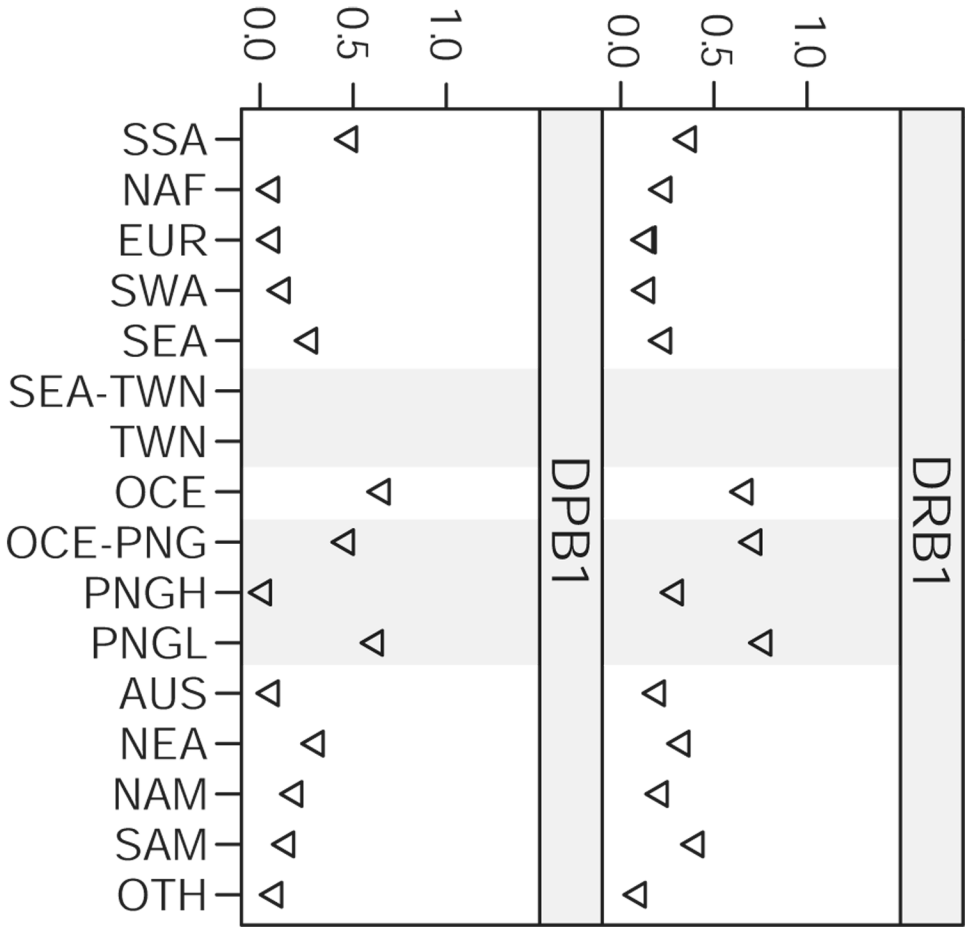

Figure 8. Genetic differentiation present in world regions and subregions

Figure 9. Global frequency distribution of the DRB1*1501 allele

Distribution was inferred from 224 population samples, indicated by the plotted points. The shaded regions indicate interpolated allele frequency; crosshatched areas are too far from a sampled population to permit meaningful frequency estimation. Only non-migrant populations were used to generate this map. Frequency maps for all alleles at all loci are available at http://www.pypop.org/popdata/.

Table 1

Results for all loci and geographic regions.

	reg [1]	m (m_l,m_w,m_a) [2]	$\bar{k}$, k_{sum} [3]	$\overline{F_{nd}}$	SE [4]	F_{nd}<0 [5]	% sig [6]	*t*-test *p* [7]	sign test *p* [7]
HLA-A	SSA	13 (4,9,0)	27, 66	−1.05	0.11	100%	38%	**3.0E−07**	**2.4E−04**
	NAF	6 (2,4,0)	24, 39	−0.61	0.13	100%	0%	**3.9E−03**	3.1E−02
	EUR	18 (4,8,6)	24, 66	−0.14	0.08	67%	0%	9.6E−02	2.4E−01
	SWA	19 (7,9,3)	20, 74	−0.8	0.17	84%	32%	**1.7E−04**	**4.4E−03**
	SEA	30 (5,25,0)	13, 65	−0.09	0.14	63%	0%	5.4E−01	2.0E−01
	OCE	16 (8,8,0)	8, 29	−0.37	0.21	75%	0%	9.0E−02	7.7E−02
	AUS	4 (0,4,0)	8, 12	−0.42	0.45	75%	0%	3.6E−01	6.2E−01
	NEA	18 (9,9,0)	22, 119	−0.24	0.3	78%	0%	4.3E−01	3.1E−02
	NAM	9 (1,8,0)	12, 34	−0.28	0.31	78%	0%	3.7E−01	1.8E−01
	SAM	10 (6,3,1)	9, 30	−0.55	0.26	70%	10%	5.1E−02	3.4E−01
	OTH	11 (3,6,2)	29, 63	−0.66	0.24	82%	27%	1.5E−02	6.5E−02
	ALL	154 (49,93,12)	18, 165	−0.42	0.07	77%	10%	**1.7E−09**	**2.2E−11**
HLA-C	SSA	10 (2,8,0)	20, 35	−1.06	0.13	100%	40%	**1.6E−05**	**2.0E−03**
	NAF	5 (3,2,0)	17, 24	−0.99	0.21	100%	40%	**6.6E−03**	6.2E−02
	EUR	11 (2,6,3)	20, 33	−1.21	0.06	100%	55%	**7.1E−10**	**9.8E−04**
	SWA	16 (5,7,4)	20, 57	−0.82	0.13	94%	19%	**1.4E−05**	**5.2E−04**
	SEA	25 (3,21,1)	14, 46	−0.89	0.14	88%	20%	**1.2E−06**	**1.6E−04**
	OCE	12 (8,4,0)	11, 28	−0.71	0.2	92%	25%	**3.7E−03**	**6.3E−03**
	AUS	4 (0,4,0)	10, 16	−1.04	0.2	100%	25%	**8.8E−03**	1.2E−01
	NEA	12 (8,4,0)	19, 42	−1.33	0.07	100%	75%	**6.7E−10**	**4.9E−04**
	NAM	7 (1,6,0)	14, 30	−0.51	0.26	71%	14%	7.6E−02	4.5E−01
	SAM	5 (2,3,0)	6, 10	−0.89	0.32	80%	20%	3.5E−02	3.8E−01
	OTH	7 (1,4,2)	24, 44	−0.91	0.15	100%	29%	**6.1E−04**	1.6E−02
	ALL	114 (35,69,10)	16, 77	−0.94	0.05	93%	32%	**1.1E−35**	**5.7E−23**
HLA-B	SSA	13 (4,9,0)	36, 108	−0.97	0.11	100%	23%	**6.1E−07**	**2.4E−04**
	NAF	5 (1,4,0)	30, 54	−1.09	0.17	100%	40%	**2.0E−03**	6.2E−02
	EUR	19 (5,8,6)	39, 120	−0.75	0.12	89%	21%	**7.0E−06**	**7.3E−04**
	SWA	18 (4,9,5)	29, 132	−0.82	0.11	94%	11%	**7.5E−07**	**1.4E−04**

	reg [1]	m (m_l,m_w,m_a) [2]	$\bar{k}$, k_{sum} [3]	$\overline{F_{nd}}$	SE [4]	F_{nd}<0 [5]	% sig [6]	*t*-test *p* [7]	sign test *p* [7]
	SEA	30 (5,24,1)	26, 128	−0.46	0.14	80%	7%	**1.9E−03**	**1.4E−03**
	OCE	13 (8,5,0)	17, 65	−0.59	0.21	92%	8%	1.1E−02	**3.4E−03**
	AUS	4 (0,4,0)	14, 27	−0.72	0.27	100%	25%	5.4E−02	1.2E−01
	NEA	16 (9,7,0)	36, 178	−0.7	0.33	94%	38%	4.1E−02	**5.2E−04**
	NAM	10 (2,8,0)	21, 79	−0.27	0.17	70%	0%	1.2E−01	3.4E−01
	SAM	8 (4,3,1)	22, 67	−0.51	0.18	88%	0%	1.7E−02	7.0E−02
	OTH	10 (3,6,1)	48, 117	−0.97	0.11	100%	20%	**5.1E−06**	**2.0E−03**
	ALL	146 (45,87,14)	30, 295	−0.68	0.06	90%	16%	**2.2E−23**	**2.7E−24**
HLA-DRB1	SSA	9 (3,5,1)	23, 68	−0.62	0.18	89%	22%	**5.7E−03**	3.9E−02
	NAF	15 (5,9,1)	27, 62	−0.63	0.1	93%	0%	**8.6E−06**	**9.8E−04**
	EUR	55 (26,13,16)	29, 110	−0.76	0.06	93%	7%	**2.3E−18**	**2.0E−11**
	SWA	9 (4,5,0)	25, 51	−0.92	0.13	100%	22%	**8.5E−05**	**3.9E−03**
	SEA	39 (14,23,2)	20, 76	−0.88	0.08	90%	23%	**2.2E−13**	**3.4E−07**
	OCE	43 (37,6,0)	13, 50	−0.42	0.15	72%	12%	**8.0E−03**	**5.4E−03**
	AUS	2 (0,2,0)	17, 24	−0.15	0.88	50%	0%	8.5E−01	1.00E+00
	NEA	41 (31,10,0)	24, 135	−0.87	0.17	93%	39%	**5.0E−06**	**1.0E−08**
	NAM	14 (5,9,0)	14, 44	−0.32	0.21	79%	7%	1.3E−01	5.7E−02
	SAM	19 (8,7,4)	13, 42	−0.37	0.16	74%	11%	3.3E−02	6.4E−02
	OTH	12 (4,3,5)	36, 66	−1.25	0.06	100%	50%	**4.9E−10**	**4.9E−04**
	ALL	258 (137,92,29)	22, 189	−0.70	0.05	87%	18%	**3.1E−37**	**1.7E−35**
HLA-DQA1	SSA	10 (2,4,4)	7, 8	−1.33	0.05	100%	50%	**2.7E−10**	**2.0E−03**
	NAF	7 (2,5,0)	7, 8	−1.33	0.09	100%	29%	**4.0E−06**	1.6E−02
	EUR	61 (37,11,13)	7, 8	−1.4	0.04	100%	61%	**1.5E−44**	**8.7E−19**
	SWA	9 (4,2,3)	7, 8	−1.44	0.05	100%	67%	**2.6E−09**	**3.9E−03**
	SEA	7 (4,1,2)	8, 8	−1.48	0.04	100%	100%	**2.3E−08**	1.6E−02
	OCE	18 (11,4,3)	6, 8	−0.9	0.1	100%	6%	**6.7E−08**	**7.6E−06**
	AUS	2 (0,2,0)	6, 7	−1.44	0.19	100%	50%	6.0E−02	5.0E−01
	NEA	31 (22,5,4)	7, 8	−1.08	0.08	97%	29%	**1.7E−14**	**3.0E−08**
	NAM	15 (3,9,3)	5, 7	−0.96	0.12	93%	0%	**8.4E−07**	**9.8E−04**
	SAM	21 (8,7,6)	5, 7	−0.9	0.12	100%	10%	**1.8E−07**	**9.5E−07**

	reg [1]	m (m_l,m_w,m_a) [2]	$\bar{k}$, k_{sum} [3]	$\overline{F_{nd}}$	SE [4]	F_{nd}<0 [5]	% sig [6]	*t*-test *p* [7]	sign test *p* [7]
	OTH	10 (4,2,4)	7, 8	−1.46	0.06	100%	80%	**1.4E−09**	**2.0E−03**
	ALL	191 (97,52,42)	7, 8	−1.21	0.03	99%	41%	7.6E−96	**1.2E−53**
HLA-DQB1	SSA	8 (1,5,2)	13, 19	−0.95	0.13	100%	12%	**1.3E−04**	**7.8E−03**
	NAF	13 (5,8,0)	14, 21	−0.64	0.1	100%	8%	**2.7E−05**	**2.4E−04**
	EUR	54 (31,13,10)	13, 19	−1.08	0.04	100%	33%	**9.1E−31**	**1.1E−16**
	SWA	7 (3,3,1)	13, 18	−1.1	0.1	100%	29%	**2.8E−05**	1.6E−02
	SEA	22 (15,5,2)	13, 24	−1.04	0.11	95%	50%	**2.1E−09**	**1.1E−05**
	OCE	23 (17,6,0)	10, 17	−0.77	0.13	87%	17%	**4.8E−06**	**4.9E−04**
	AUS	2 (0,2,0)	9, 12	−0.78	0.12	100%	0%	6.8E−02	5.0E−01
	NEA	33 (24,6,3)	11, 20	−0.8	0.13	82%	36%	**3.4E−07**	**3.2E−04**
	NAM	13 (4,9,0)	7, 17	−0.41	0.17	69%	0%	2.5E−02	2.7E−01
	SAM	19 (10,7,2)	6, 15	−0.61	0.15	79%	5%	**4.0E−04**	1.9E−02
	OTH	8 (4,2,2)	12, 17	−1.11	0.06	100%	38%	**3.0E−07**	**7.8E−03**
	ALL	202 (114,66,22)	11, 30	−0.87	0.04	91%	26%	**1.9E−58**	**7.7E−36**
HLA-DPA1	SSA	7 (6,1,0)	5, 8	−1.36	0.12	100%	29%	**1.8E−05**	1.6E−02
	NAF	0 (0,0,0)	NA	NA	NA	NA	NA	NA	NA
	EUR	10 (9,1,0)	3, 7	−0.09	0.26	60%	0%	7.1E−01	7.5E−01
	SWA	1 (1,0,0)	5, 5	−0.48	NA	100%	0%	NA	NA
	SEA	2 (2,0,0)	4, 5	−1.02	0.68	100%	0%	2.8E−01	5.0E−01
	OCE	10 (4,5,1)	4, 5	−0.67	0.17	80%	0%	**2.4E−03**	1.1E−01
	AUS	0 (0,0,0)	NA	NA	NA	NA	NA	NA	NA
	NEA	4 (1,2,1)	4, 5	−0.6	0.47	75%	0%	2.4E−01	6.2E−01
	NAM	5 (0,2,3)	3, 4	0.93	0.07	0%	0%	**1.2E−04**	6.2E−02
	SAM	5 (4,1,0)	2, 3	−1.06	0.14	100%	0%	**1.2E−03**	6.2E−02
	OTH	1 (1,0,0)	5, 5	−1.27	NA	100%	0%	NA	NA
	ALL	45 (28,12,5)	4, 9	−0.53	0.13	73%	4%	**1.1E−04**	**2.5E−03**

	reg [1]	m (m_l,m_w,m_a) [2]	$\bar{k}$, k_{sum} [3]	$\overline{F_{nd}}$	SE [4]	F_{nd}<0 [5]	% sig [6]	*t*-test *p* [7]	sign test *p* [7]
HLA-DPB1	SSA	13 (8,3,2)	16, 43	0.13	0.35	69%	8%	7.1E−01	2.7E−01
	NAF	3 (2,1,0)	17, 22	−0.38	0.17	100%	0%	1.2E−01	2.5E−01
	EUR	41 (32,5,4)	16, 52	0.29	0.09	32%	0%	**1.6E−03**	2.8E−02
	SWA	3 (2,1,0)	15, 26	0.77	0.44	0%	0%	1.6E−01	2.5E−01
	SEA	17 (15,2,0)	14, 43	−0.08	0.23	59%	6%	7.4E−01	6.3E−01
	OCE	20 (14,5,1)	9, 31	0.02	0.19	60%	0%	9.1E−01	5.0E−01
	AUS	2 (0,2,0)	8, 10	−0.05	0.31	50%	0%	8.5E−01	1.00E+00
	NEA	13 (5,5,3)	12, 25	−0.53	0.09	92%	0%	**7.6E−05**	**3.4E−03**
	NAM	7 (0,7,0)	7, 14	0.56	0.51	43%	0%	2.8E−01	1.00E+00
	SAM	21 (16,4,1)	5, 19	−0.39	0.21	67%	5%	7.9E−02	1.9E−01
	OTH	7 (6,1,0)	17, 25	−0.09	0.2	57%	0%	6.4E−01	1.00E+00
	ALL	147 (100,36,11)	12, 67	0.01	0.07	55%	2%	8.5E−01	2.5E−01

[1] See text for three-letter abbreviations of world regions. ALL indicates all populations.

[2] m: Total number of populations sampled (m_l: number of populations from the literature dataset; m_w: number of populations from the workshop dataset; m_a:number of populations from the AlleleFrequencies.net dataset).

[3] $\bar{k}$: Average number of observed distinct alleles in each region. k_{sum}: Total number of observed distinct alleles across all populations in an entire region. A “distinct allele” is defined as having a distinct peptide sequence across exons 2 and 3 (for class I) or exon 2 (for class II). For comparison, by this definition, the total number of known distinct alleles in release 2.18 of the IMGT/HLA database is as follows: A, 481; C, 250; B, 806; DRB1, 418; DQA1, 14; DQB1, 63; DPA1, 14; DPB1, 113.

[4] Standard error of mean F_{nd} estimate.

[5] Percentage of populations with a negative F_{nd} value.

[6] Percentage of populations with a significantly negative F_{nd} value, as tested by Slatkin’s implementation of the Monte Carlo approximation of the Ewens-Watterson exact test, using a two-tailed test ($p < 0.05$) of the null hypothesis of neutrality.

[7] p-values less than 0.01 are in boldface.