Associations of HLA-A, HLA-B and HLA-C Alleles Frequency with Prevalence of Herpes Simplex Virus Infections and Diseases Across Global Populations: Implication for the Development of an Universal CD8+ T-Cell Epitope-Based Vaccine

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Abstract

A significant portion of the world's population is infected with herpes simplex virus type 1 and/or type 2 (HSV-1 and/or HSV-2), that cause a wide range of diseases including genital herpes, oro-facial herpes, and the potentially blinding ocular herpes. While the global prevalence and distribution of HSV-1 and HSV-2 infections cannot be exactly established, the general trends indicate that: (*i*) HSV-1 infections are much more prevalent globally than HSV-2; (*ii*) Over half billion people worldwide are infected with HSV-2; (*iii*) the sub-Saharan African populations account for a disproportionate burden of genital herpes infections and diseases; (*iv*) the dramatic differences in the prevalence of herpes infections between regions of the world appear to be associated with differences in the frequencies of human leukocyte antigen (HLA) alleles. The present report: (*i*) analyzes the prevalence of HSV-1 and HSV-2 infections across various regions

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of the world; (*ii*) analyzes potential associations of common HLA-A, HLA-B and HLA-C alleles with the prevalence of HSV-1 and HSV-2 infections in the Caucasoid, Oriental, Hispanic and Black major populations; and (*iii*) discusses how our recently developed HLA-A, HLA-B, and HLA-C transgenic/H-2 class I null mice will help validate HLA/herpes prevalence associations. Overall, high prevalence of herpes infection and disease appears to be associated with high frequency of HLA-A*24, HLA-B*27, HLA-B*53 and HLA-B*58 alleles. In contrast, low prevalence of herpes infection and disease appears to be associated with high frequency of HLA-B*44 allele. The finding will aid in developing a T-cell epitope-based universal herpes vaccine and immunotherapy.

INTRODUCTION

A significant portion of the world's population is infected with herpes simplex virus type 1 and/or type 2 (HSV-1 and/or HSV-2) [1-3]. Herpes is epidemic in some regions and ethnicities of the world but is at its lowest prevalence in other regions and ethnicities (Fig. 1 and Table 1). For instance, a high HSV-2 prevalence of 39.2% is recorded among Non-Hispanic Blacks while a low prevalence of 12.3% is recorded among Non-Hispanic Whites. While the exact estimates of HSV-1 and HSV-2 prevalence in the world are limited by poor availability of sero-epidemiological data, general trends indicate that HSV-2 infections continue to spread globally: (*i*) HSV-2 now affects over 540 million people, aged 14-49 years, worldwide, with an estimate of 23.6 million people newly infected per year [1-4]; (*ii*) In the United States, about one in six individuals from the sexually active population (i.e. between 14 and 49 years of age) are infected with HSV-2, which is equivalent to approximately 60 million people, with the highest prevalence among non-Hispanic black individuals and the lowest among those of Asian descent; (*iii*) globally, more women are infected by HSV-2 than men [4, 5]; (*iv*) the number of infected men and women increases with age [4]; (*v*) although the prevalence of herpes infection varies substantially by region, it is mostly higher in developing than in developed regions; (*vi*) HSV-2 and HSV-1 prevalence varies markedly by country, by region within country, and by population subgroup [6]; (*vii*) globally, genital herpes caused by HSV-2 is particularly frequent in sub-Saharan Africa, countries form Latin America, and South East Asia, with greater than 20% of the populations in the sub-regions suffering from genital herpes infection [6]. In contrast, the lowest HSV-2 prevalence is recorded in Western and Southern Europe, Middle East, North Africa, Japan, Australia and New Zealand, with less than 10% of the populations in the sub-regions exhibiting HSV-2 infection [6, 7]. Countries from central Europe and North America have an intermediate 11-20% HSV-2 prevalence [4] (Fig. 1 and Table 1); (*viii*) HSV-1 infections, acquired during childhood and adolescence [6], are globally, much more prevalent than HSV-2 [7], causing significant morbidity especially among young adults in western societies, where up to 80% are sero-positive; (*ix*) HSV-2, but not HSV-1, leads to two- to three-fold increase in risk of HIV-1 infection, supported by an increase in prevalence of both HSV-2 and HIV-1 in the same regions of sub-Saharan African regions [8-12]; (*x*) HSV-1 and HSV-2 infections are a large and worldwide public health problem [11, 13-17]. In addition to causing genital herpes and oro-facial herpes (i.e. cold sores), HSV-1 and HSV-2 also cause encephalitis and death in newborns due to vertical transmission, while HSV-1 causes blinding ocular herpes [18, 19]. In the United States, over 400,000 individuals

have a history of ocular herpes disease caused by HSV-1; and finally; (*xi*) there is no vaccine available today to protect against HSV-1 or HSV-2 infection and disease, and patients must rely on sustained or intermittent antiviral drugs (Acyclovir and derivatives) [20, 21]; (*xii*) the association of the prevalence of HSV-1 & HSV-2 infections and diseases with the frequency of human leukocyte antigens (HLA) alleles is not fully elucidated. While a handful of studies point to association trends between the frequency of some common HLA class I alleles and the high/low prevalence of genital HSV-2 infection/disease, few studies have reported association of HLA alleles with infection and severity of ocular HSV-1 infection and disease, such as recurrent herpetic stromal keratitis (rHSK), the most common cause of cornea-derived blindness in developed nations [13, 17, 22-28].

Six co-dominantly expressed HLA class I alleles are encoded by three loci (HLA-A, -B, and -C). The frequency of HLA class I alleles differ significantly among the four major world's populations (i.e. Caucasoids, Orientals, Hispanics and Blacks) as the HLA system is the most polymorphic of all human genetic systems [29]. Many DNA-defined alleles with identical serotypes may have variable frequencies in different populations [29]. About 7000 HLA-I polymorphisms have been reported to date (http://hla.alleles.org/). Each HLA class I molecule has a distinct peptide binding specificity. As a result, HLA-I/peptide complexes that drive the expansion of pathogen-specific CD8$^+$ T cells are extremely diverse in each individual. However, it is possible to account for the predominance of all known HLA class I with only eleven main functional binding specificities.

This report will: (*i*) analyze the existing literature depicting prevalence of HSV-1 and HSV-2 infections across various human populations (Fig. 1); (*ii*) provide a comparative review of potential associations of the most common HLA-A, HLA-B and HLA-C alleles with prevalence of HSV-1 and HSV-2 infections and diseases in the four major world's populations (i.e. Caucasoids, Orientals, Hispanics and Blacks) (Fig. 2 and Table 2 to 4); and (*iii*) discuss how our recently developed HLA-A*01:03, HLA-A*24:02, HLA-B*08:01, HLA-B*27:05, HLA-B*35:01, HLA-B*44:02 and HLA-C*07:01 monochain transgenic/H-2 class I null mice, will help validate these associations and aid in developing a universal T-cell epitope-based herpes vaccine that would provide a broad coverage of human population, regardless of race and ethnicity.

MATERIALS AND METHODS

1. Analyses of potential association of the HLA with high vs. low prevalence of herpes

HLA genes are involved in inducing either susceptibility or resistance to many infectious diseases [30-34]. In order to disentangle the respective contribution of the HLA-A, HLA-B and HLA-C alleles in HSV-1 and HSV-2 infections: (1) We performed a systematic haplotypic analysis in the four major world's populations (Caucasoids, Orientals, Hispanics and Blacks), which display various prevalence of HSV-1 and HSV-2 infection; (2) PubMed® (1966-present) was used to identify cross-sectional studies with HSV-1 and HSV-2 sero-prevalence data and to identify the highest HLA class I allele that are specific to distinct populations with low vs. high prevalence of HSV-1 and HSV-2 infections; (3) The potential association of the HLA class I alleles [35-37] with high vs. low prevalence of herpes infections (which can be translated into "herpes susceptibility or resistance") was

then determined. For the HLA frequency in ethnically and geographically distinct populations; the databases from the following websites were consulted: http://www.ncbi.nlm.nih.gov/projects/gv/mhc/ [38, 39], http://www.allelefrequencies.net/default.asp [38, 39], and http://hla-net.eu [40-42].

2. Statistical analyses

Data for each assay were compared by analysis of variance (ANOVA) and Student's t-test using Graph Pad Prism 5 software (San Diego, CA). Differences between the groups were identified by ANOVA, multiple comparison procedures, as we previously described [14, 24, 25, 27, 43-54]. Statistical analysis also included Fisher's exact test and multivariate analyses, using logistic and linear regression models. Results are considered statistically significant if $p < 0.05$.

RESULTS & DISCUSSIONS

1. A comparative review of HLA-A, HLA-B, and HLA-C associations with prevalence of HSV-1 and HSV-2 infections and diseases across various human populations (Fig. 2 and Table 2 to 4)

The clinical spectrum of HSV-1 & HSV-2 infections, ranging from asymptomatic to frequently distressing symptomatic outbreaks appear to be associated with HLA class I molecules [55-57]. These associations suggest that CD8^{+} T cell-mediated immune mechanism(s), influenced by HLA class I genes at the A, B, and C main loci, may influence the outcome of recurrent herpes infections and diseases [14, 58]. The HLA-B locus is the most polymorphic, with 1795 known proteins, followed by HLA-A with 1290, and HLA-C with 946 [58]. Genetic variation within the highly polymorphic HLA class I region contributes to the diversity of viral pathogens recognized by CD8^{+} T cells [59, 60]. The dramatic differences in the prevalence of HSV-1 and HSV-2 between regions of the world prompted us to explore potential associations between frequencies of most common HLA-A, HLA-B, and HLA-C alleles and prevalence of HSV-1 and HSV-2 infections and diseases (i.e., "resistance vs. susceptibility" to infections and diseases) [56].

α) HLA-A—HLA-A*01: According to the Allele Frequency website [39, 61], HLA-A*01 is highly represented in the sub-Saharan populations. For instance, the HLA-A*01:03 allele is one of the most frequent alleles in Ethiopia. Thus, the HLA-A*01 allele appears to be linked with high prevalence to genital herpes disease. However, HLA-A*01 is also the most frequent allele in North Africans where genital herpes is not that endemic. For instance, 25.6% of Moroccans, who have one of the lowest rate of genital herpes, express the HLA-A*01 allele [62-65]. Spain and Israeli populations, which have one of the lowest rates of herpes infection in the world, also express a high frequency of the HLA-A*01 allele [66]. About 33.6% of Australians, which also have one of the lowest rates of herpes, express the HLA-A*01 allele [67, 68]. Thus, HLA-A*01 allele may not be considered as a factor in resistance/susceptibility to herpes.

HLA-A*02 allele has become an important target for T cell-based herpes immunotherapy reflecting its high prevalence in most populations worldwide, regardless of race and

ethnicity [69-72]. HLA-A*0201 subtype is highly represented in human population regardless of race and ethnicity [39, 61]. HLA-A*0201 is also highly represented in sub-Saharan populations with up to 50% of the population in Cameroun expressing this haplotype [73]. In Kenya, where 20% of individuals are affected by genital herpes disease, 51% of individuals express the HLA-A*0201 subtype [38, 39]. In Senegal, where both HSV-1 and HSV-2 are endemic, up to 68% of the population express HLA-A*0201. However, the Australian population, which has one of the lowest rates of herpes, 46.5% of individuals express the HLA-A*0201 allele [67, 68]. Similarly, 50% of Belgians and 32.4% of Moroccans, both exhibit low rates of herpes infection, express the HLA-A*0201 allele [62-65, 74-77]. Thus, it is unclear whether HLA-A*0201 is a factor in resistance/ susceptibility to herpes.

Of those tested positive for HSV-1 and HSV-2 infection, up to 90% said a health-care professional had never told them that they had genital herpes, ocular or oro-facial herpes (Asymptomatic individuals, ASYMP). The remaining 10% are symptomatic individuals (SYMP) often-express herpetic disease, some of them multiple times a year. In a recent study [78], we performed HLA-A*02 sub-typing of HSV-1 seropositive symptomatic (SYMP) vs. asymptomatic (ASYMP) individuals using SSP genotyping [79]. The results showed that all, but one of the HLA-A*02 individuals in our cohort were of the HLA-A*02:01 subtype, with the remaining (SYMP) individual of the HLA-A*02:06 subtype. Although each HLA-A*02 subtype molecule can be expected to have a unique specificity, large overlaps in the repertoires of HLA-A*02 molecules have been reported [72]. Indeed, over 70% of the peptides that bind HLA-A*02:01, the most common HLA-A*02 subtype, with high affinity were found to also bind at least two other of the 4 next most common HLA-A*02-subtypes, including the HLA-A*02:06 subtype [72]. Thus, HLA-A*02:01-restricted epitopes may be useful in vaccine studies with individuals expressing alleles other than HLA-A*02:01. At the same time, however, while cross-reactivity at the binding level appears to be particularly high in the case of HLA-A*02, it must also be noted that differences between the molecules may encompass residues at positions involved in TCR recognition, and thus may be associated with differences that lead to divergence in T cell repertoires.

HLA-A*24 is the most frequently represented allele of the HLA-A locus in sub-Saharan African countries, where the highest prevalence of herpes infection and disease is recorded. HLA-A*24 is frequent in Cameroun and Guinea populations with the highest worldwide prevalence of both HSV-1 and HSV-2 infections [39]. In Cameroun, where the HSV-2 infection rate is at 55% for women and 36% for men, HLA-A*24 is the third most frequent allele of the HLA-A locus (after A*33 and A*30) [73]. The population of Costa Rica, which has one the highest rates of genital herpes in the world (39% in women) also has HLA-A*24 as the second most frequent allele, after HLA-A*02 [80]. HLA-A*24 is also frequent in some Asian populations where a high prevalence of HSV-2 infection is also recorded. For instance, HLA-A*24 is highly represented in individuals from China [81, 82] and represented in up to 48.9% of individuals from Taiwan [83]. In populations from Eastern Asia (Brunei Darussalam, China, Democratic People's Republic of Korea, Mongolia, Republic of Korea, Singapore), where 61.8% of females aged 15-49 and 47.8% of males

aged 15-49 are seropositive for HSV-2, HLA-A*24 is the most frequent HLA-A allele [4]. HLA-A*24 is also the most frequent HLA-A allele in South East Asian populations with HLA-A*02 and HLA-A*11 as the 2nd and 3rd most frequent alleles. HLA-A*24:02 is one of the most common HLA subtypes in Southeast Asian populations (29.9%) [84]. HLA-A*24 is the most frequent allele of the HLA-A locus in Colombian black and Mestizos ethnic groups of the population where one of the highest prevalence of genital HSV-2 infection is recorded (50% in women) [85, 86]. In contrast, this haplotype is not well represented in North African countries with the lowest rate of herpes infection. HLA-A*24 is not frequent in the United Kingdom where one of the lowest rate of genital herpes is recorded [87] (i.e. the sixth most frequent after HLA-A*01, HLA-A*02, HLA-A*03, HLA-A*11 and HLA-A*23). Thus, overall, it appears that the high frequency of HLA-A*24 allele positively correlates with high prevalence of HSV-2 infection in the world populations (Table 2B).

β) HLA-B—HLA-B*07 is the most frequent allele of HLA-B locus in Spain [87, 88], Germany [87, 89] and the United Kingdom, where some of lowest rates of genital herpes are recorded. However, HLA-B*07 is also a frequent allele in the sub-Saharan population where herpes infection is endemic [87]. For instance, between 9 and 19% of individuals from South Africa, depending on ethnicity, and 13% of Kenyans express the HLA-B*07:02 subtype [38, 39]. South African and Kenyan populations have one of the highest rates of herpes in the world. This suggests that HLA-B*07 might not be a factor in resistance/susceptibility to herpes infection.

The **HLA-B*08** allele is more common in many populations of African ancestry who continue to account for a disproportionate burden of the HSV-1 and HSV-2 epidemic. For instance, up to 29% of Senegalese express HLA-B*08, and 14% of individuals from South Africa Natal Zulu express the HLA-B*08:01 subtype. However, HLA-B*08 is also frequent in many western nations where the frequency of herpes in lowest. For instance HLA-B*08:01 subtype is represented in up to 35% of some Caucasoid western European populations [90-92]. This suggests that HLA-B*08 might not be a factor in resistance/susceptibility to herpes infection.

The **HLA-B*15** allele is also highly represented in sub-Saharan populations that have the highest rates of HSV-1 and HSV-2 infections in the world. For instance, HLA-B*15:03 subtype is the highest alleles of the HLA-B locus expressed by 30% South Africans [93]. Up to 20% of Cameroonians express HLA-B*15 [73, 94]. HLA-B*15:03 is also the third highest alleles of the HLA-B locus (after HLA-B*42:01 and HLA-53:01) in Zambia [95]. 15.5% of Costa Ricans, which have one the highest rates of genital herpes in the world (39% in women), express the HLA-B*15 allele [80]. HLA-B*15 is also the most frequent allele of the HLA-B locus in the Colombian black ethnic group with one of the highest prevalence of genital herpes (50% in women) [85, 86, 96]. HLA-B*15 allele is also the second most frequent allele of the HLA-B locus (after HLA-B*53) in non-Hispanic African Americans (22.3%), a population with high rate of HSV-2 infection [97-100]. HSV-2 sero-prevalence is approximately three times greater among non-Hispanic blacks in the US (~39.2%) compared to non-Hispanic whites (~12.3%) [101]. However, HLA-B*15 is also the most frequent allele of HLA-B locus in the Japanese population, known for the lowest rates of genital herpes [102]. HLA-B*15 is also the most frequent allele of HLA-B locus in Bangladesh,

also know for one of the lowest rates of herpes in the world [103]. Thus, the frequency of HLA-B*15 allele does not appear to correlate with prevalence of HSV-1 and HSV-2 epidemic, suggesting that this allele may not be associated to susceptibility to herpes infection and disease.

The **HLA B*27** appears to promote recurrence of herpetic eye disease caused by HSV-1 infection [57]. Recurrent herpetic stromal keratitis (rHSK), caused by spontaneous reactivation of HSV-1 from latently infected neurons of the trigeminal ganglia, is the most common cause of cornea-derived blindness in developed Western nations [13, 17, 22-28]. Interestingly, in developed Western nations, where rHSK is more prevalent, the HLA-B*27 allele is more frequent in Caucasoid populations than in North Africans (4%), Chinese (2.9%), and Japanese (0.1-0.5%) descent. For instance, 24% of northern Scandinavian [104, 105], 16% of Swedish [106-109], 14.3% of Belgium [74], 13% of German [110, 111], 12% of French [112-115], 11.2% of Romanian [116-121], 10.2% of Russian [122] populations express HLA-B*27 allele. HLA-B*27 allele is, overall, not frequent in Oriental populations, except for Taiwanese where this allele is highly frequent (15%). For instance, HLA-B*27 allele is < 3% in Chinese Tibet, Southwest and North regions and Yannan Province [93, 123-125]. Only 3% of HLA-B*27 allele is detected in Black Sub-Saharan population [126-129] and African-American populations [130, 131]. The frequency of HLA-B*27 allele is also low in Arab (<3%) [132-139] and Israel Jewish populations (3.4%) [140]. One of the lowest frequencies of HLA-B*27 allele is detected in Hispanic (<2%) [100, 141-144], Mongolian (<2%) [145], Japanese (<2%) [146], Singaporean Chinese (<2%) [93, 123, 124, 147-149], and in Korean (<2%) populations [150-155]. A genital herpes study comparing HLA frequencies among HSV-seronegative individuals, HSV-2 seropositive "asymptomatic" individuals and HSV-2 seropositive symptomatic individuals reported an association between HLA-B*27 high frequency and an increase in symptomatic genital herpes infection [56]. HLA-B*27 is the second most frequent allele of the HLA-B locus in Burkina Faso where herpes is endemic [156]. HLA-B*27:05 is represented less than 8% of the Caucasian populations where herpes not endemic [97, 157]. The HLA-B*27 allele is associated with exacerbation of herpes disease. While HLA-B*27 allele is ubiquitous in the world population, it is significantly more common in herpes endemic regions than in non-endemic regions, suggesting that the HLA-B*27 allele is associated with herpes infection and disease. This suggests that HLA-B*27 might be a factor of susceptibility to genital (Table 2B) and ocular herpes infection and disease (not shown). Since HLA-B*27:05 monochain transgenic/H-2 class I null mice are now available [158], it would be interesting to see whether these mice will be more susceptible to genital and ocular herpes infection and disease.

HLA-B*35 association with prevalence of herpes infection and disease is rather controversial. HLA-B*35 expression has been previously linked with resistance to recurrent herpes labialis in HSV-1 seropositive individuals (cold sores) [159, 160]. Inversely, a low expression of HLA-B*35 was associated with a significant increase in symptoms from recurrent herpes [159, 160]. However, high frequency of the HLA-B*35 in herpes endemic populations appears to be associated with high prevalence of HSV-2 infection. Particularly, HLA-B*35 is the most frequent allele of HLA-B locus in population from Costa Rica

(31.5% of Costa Ricans express this allele), which have one the highest rate of genital herpes in the world (39% in women) [80]. HLA-B*35 is also a frequent allele in South America, where a moderate prevalence of genital HSV-2 infection is recorded [6, 7]. However, HLA-B*35 is also well represented in the Middle East populations where the rates of genital herpes are one of the lowest in the world. High frequency of HLA-B*35 is also detected in Bangladesh [103], North Africa [64], Corsica [161, 162] and Israel [140] all of these regions have the low rate of genital herpes. HLA-B*35 is the most frequent allele of the HLA-B locus (28.8 %) in the Iranian population which has one of the lowest rate of herpes [163]. Inversely, low frequency of HLA-B*35 haplotype was detected in Australians adults who also have one of the lowest prevalence of HSV-2 infection (12%) [7]. We should emphasize that: (1) HLA-B*35 is associated with increased susceptibility to HIV-1 infection; (2) a rapid progression of HIV-1 [164, 165] and HIV-2 [166] infections to AIDS; and (3) genital herpes is associated with a two- to three-fold increase in risk of HIV-1 infection in sub-Saharan African population. Thus, it is likely that a negative immuno-synergy occurs between the two sexually transmitted viruses (HIV-1 and HSV-2) in HLA-B*35 positive individuals from the same sub-Saharan region.

HLA-B*44 is the most frequent allele of HLA-B locus in Caucasoid European population. Thus, HLA-B*44 expression may positively correlate with low prevalence of HSV-2 infection known in European populations. For instance, 35.7% of North Ireland [93, 124, 147] and 32% of English [167] populations that have low frequency of herpes infection express the HLA-B*44 allele. HLA-B*44 is the most frequent allele of the HLA-B locus in French [112-115] Spanish [168] and Basques Caucasoid populations [169, 170], which have some of the lowest rates of herpes infection and disease. HLA-B*44 is also frequent in North African [64], Bangladeshi [103], Japanese [171] and Israeli [140] populations, which have some of the lowest rates of genital herpes. In contrast, the HLA-B*44 is not frequent in sub-Saharan Africans, where the prevalence of HSV-2 infection is relatively high. Thus, the high frequency of HLA-B*44 appears to positively correlate with low prevalence of HSV-2 infection and disease. This suggests that the HLA-B*44 allele may constitute an excellent marker, or a factor, of genetic resistance to herpes infection and disease (Table 2A).

The HLA-B*53 allele is the most frequent allele of the HLA-B locus in African Americans (25.5%), a population with a high rate of HSV-2 infection [97-100]. HLA-B*53 allele is also the most frequent allele in Cuban population with a highest prevalence of herpes [93, 124, 147-149]. In contrast, HLA-B*53 allele is not frequent in Caucasian and oriental populations (<3%) with a lowest rate of herpes [93, 124, 132, 172]. Thus, the high frequency of HLA-B*53 appears to positively correlate with high prevalence of HSV-2 infection and disease (Table 2B).

The HLA-B*58 allele is the most frequent HLA-B allele in South Africa (39%), Cameroun and Kenya, where HSV-2 infection rates are at 55% for women and 36% for men [73, 93, 124, 147]. HLA-B*58 is the second most frequent haplotype of the HLA-B locus (after HLA-B*15 allele), in many other sub-Saharan African countries where herpes is endemic. For instance, HLA-B*58 is the most frequent generic HLA-B type in Botswana (17.9%) [164]. HLA-B*58 is also the second most frequent allele, after HLA-B*15, in South African regions where herpes in endemic [93]. This association suggests that immunological factors

linked to HLA-B*58, such as CD8^{+} T cell responses may actually increase the risk of HSV-2 infection and disease. In contrast, the HLA-B*58 allele is not frequent in many South East Asia where the rate of genital herpes is low (compared to HLA-B*13, HLA-B*15 and HLA-B*40, the three most represented alleles) [39]. For instance, HLA-B*58 allele is at its lowest rate in individuals from Japan [173], which also have one of the lowest rate of genital herpes in the world. HLA-B*58 allele is not a frequent allele in the population of Bangladesh, where a low genital herpes infection rate of 7% was recorded in women. In western European countries that also have a low prevalence of genital herpes, such as Spain with a 3.9 prevalence of genital herpes in men, HLA-B*58 is not well represented [87, 88]. The HLA-B*58 allele is also not frequent in the Middle East countries where the rates of genital herpes is one of the lowest in the world. Thus, overall, a high frequency of HLA-B*58 allele appears to be associated with increased frequency of HSV-2 infections and diseases (Table 2B).

One should also emphasize that, among the three HLA-A, HLA-B and HLA-C alleles, the HLA-B alleles are the most associated with resistance/susceptibility to herpes. This suggests that the HLA-B locus, but not HLA-A and HLA-C, might encode for one or several immunopathological factors that would rather lead to herpes infection and diseases.

γ) HLA-C—HLA-C*02 is the most frequent allele of HLA-C locus in sub-Saharan countries known for a high rate of genital herpes, such as Burkina Faso [156, 174], Cameroun [73], Central African Republic (where 77% of the population express this allele) [94, 175]. A recent study showed an association between HLA-C*02 high frequency with an increase in herpes infection and disease [56]. However, HLA-C*02 is the second most frequent allele of the HLA-C locus in the Spanish population (7.2%, after HLA-C*07), which has one of the lowest prevalence of genital herpes in men (3.9% [87, 88]) as well as in overall Caucasoid Western Europe [110, 111]. Thus, HLA-C*02 association with prevalence of herpes infection and disease is rather controversial.

HLA-C*07 is one of the most frequent alleles of the HLA-C locus in sub-Saharan population. For instance, over 49.5% of individuals in Central African Republic express this allele and have a high prevalence of herpes. In Zambia, where the rate of genital herpes is at 55% in women and 36% in men, HLA-C*07 haplotype is the third most frequent HLA-C allele. In Cameron where HSV-2 infection rate is at 55% for women and 36% for men, HLA-C*07 is the second frequent allele of the HLA-C locus [73]. HLA-C*07 is the most highly frequent allele of HLA-C locus in population from Costa Rica, which have one the highest rate of genital herpes in the world (39% women have genital herpes) [80]. HLA-C*07 is also the most frequent allele of the HLA-C locus in Columbian black and Mestizos ethnic group of the population with one of the highest prevalence of genital herpes (50% in women) [85, 86]. However, HLA-C*07 is also a frequent allele in the European and oriental populations with ~41 % of Caucasians and 28% of Orientals expressing HLA-C*07, both known for low rates of genital herpes [176, 177]. The HLA-C*07 expression is at 60.3% in England [178-180], 66% in Poland [181], 64% in Scotland [182] and 63% in Ireland [124, 125]. The 60.3 % of England population expresses HLA-C*07 have only 4% prevalence of genital herpes HSV-2 infection. 45 % of Spanish population do express HLA-C*07 and have one of the lowest prevalence of genital herpes HSV-2 infection (4%) [87, 183-188].

HLA-C*07:01 is also the most frequent alleles of HLA-C locus in North American Caucasians (i.e. USA), European Caucasians (i.e. France) and Middle Eastern (i.e. Saudi Arabia) and North African (i.e. Morocco, Tunisia and Algeria) populations with low prevalence of genital HSV-2 infections. HLA-C*07 is also the second most represented alleles (after HLA-C*04) for the HLA-C locus in Middle-East countries, such as Syria [189], where the lowest rates of HSV-2 infection in the word are recorded. HLA-C*07 also appears to be the most frequent HLA-C allele in Latin America where a high prevalence of HSV-2 infection is recorded [4]. In addition, although HLA-C*07 is frequent in some regions of sub-Saharan Africa where genital herpes caused by HSV-2, is endemic, its frequency appears lower compared to European and north American populations [64, 95, 190-194]. For instance, in South Africa and Cameron (Swa, Pygmy and Bamileke ethnic groups) where genital herpes is endemic only 18% of the population express HLA-C*07 [195-197]. In Cameron HLA-C*07:01 is the second most frequent HLA-C allele, after HLA-C*02:01 [39]. HLA-C*07:01 is the second or third most frequent allele in Kenya after HLA-C*06:02 and HLA-C*0401 [39]. In Kenya and Zimbabwe, where the prevalence of HSV-2 infection in women is at 68% and 67%, respectively, the HLA-C*07 haplotype is not frequent in the adult population [64, 95, 190-194]. Depending on the ethnicity, HLA-C*07:01 is the second or third frequent allele in Kenya after HLA-C*06:02 and HLA-C*0401 [39]. In Cameron, Zimbabwe and Zambia, HLA-C*07:01 is the second frequent allele after HLA-C*04:01 [39]. HLA-C*07 appears to be poorly represented in Mali [39]. HLA-C*07:01 is not well represented in Burkina Faso nor in Senegal ethnic groups [39]. However, in Equatorial Guinea, Ughanda, Rowanda and Kenya HLA-C*07:01 appears to be the most frequent allele for HLA-C locus [39]. About 49.5% of the population in Central African Republic express HLA-C*07:01 [94, 175]. In Burkina Faso (Fulani ethnic group), HLA-C*07:01 is the third most frequent allele for HLA-C locus, after HLA-C*02 and HLA-C*16:02 [39]. In North-East Asia, which constitutes a region with high rates of herpes infection, the HLA-C*07 is not a frequently represented allele. Nevertheless, in Asia HLA-C*07 is the second most frequently represented allele for HLA-C locus (after HLA-C*03), and this region constitutes one of the lowest rates of herpes infection in the world. While the HLA-C*07 is highly expressed in the four major population groups (Caucasoid, Hispanics, Orientals and Blacks), its association with resistance vs. susceptibility to herpes in unclear.

In this review, we have elucidated the association of the prevalence of HSV-2 infection with HLA class I allele frequency for thirteen different HLA-A/B/C alleles (Table 4). In summary, the subset of "risk" HLA class I alleles that appears more strongly and consistently associated with high prevalence of herpes infections and diseases (i.e. susceptibility to herpes infections and diseases) included HLA-A*24, HLA-B*27, HLA-B*53 and HLA-B*58. In contrast, high frequency of HLA-B*44 allele appears to be associated with low prevalence of herpes infections and diseases (i.e. resistance to herpes infections and diseases) (Fig. 2 and Table 3). This HLA association should not be interpreted as the sole factor driving the prevalence of herpes nor should be considered as the sole cause of the susceptibility vs. resistance to herpes.

2. Associations of HLA class I haplotypes with herpetic eye disease

While a handful of studies point to an emergence of association trends between the frequency of some HLA class I alleles and the high/low prevalence of genital HSV-2 infection/disease, few studies have reported association of HLA with the prevalence of ocular HSV-1 infection or with the severity of recurrent herpetic stromal keratitis (rHSK) [13, 17, 22-28]. In an early 1970s study a significant association of HLA-B5 locus with recurrent herpes was reported [198]. However, in that study it is unclear which allele of the HLA-B5 locus is most associated with recurrent herpes. A later 1980 study showed that HLA-A*30 allele occurred three times more frequently in patients with rHSK than in those who lack the HLA-A*30 allele [199]. Note that HLA-A*30 is the second highest frequent allele of HLA-A locus in many sub-Saharan countries (where both HSV-1 and HSV-2 is endemic). For example in Cameroun, 18% of the population express HLA-A*30 [73, 94], whereas the HLA-A*30 is not frequent in the Caucasoid population where HSV-1 infections are more frequent [40-42, 200, 201]. A more recent study reported that HLA B*27 alleles promotes recurrence of HSV-1 herpetic eye disease [57]. Thus far, HLA-B5, HLA B*27 and HLA-A*30 are the only alleles reported as associated to exacerbation of recurrences of ocular herpetic eye disease [57]. However, much work is needed to investigate whether ocular herpes infection and disease are affected by HLA-A, HLA-B and HLA-C alleles. We are in the process of evaluation whether HLA-B*27:05 monochain transgenic/H-2 class I null mice, recently developed, will be more susceptible to ocular herpes infection and disease.

3. How would the knowledge of association of HLA frequency with herpes prevalence help develop a universal T cell epitope-based herpes vaccine?

T cell responses to peptide epitope-based vaccines are dependent on HLA molecules, which play a pivotal role in the selection of the T cell repertoire in the thymus and presentation of "protective" and "pathogenic" HSV T cell epitopes in the periphery. Although many HLA-A*0201-restricted epitopes have been identified from HSV-1 and HSV-2 protein antigens, a question of practical importance is the translation of these pre-clinical findings based solely on HLA-0201-restricted epitopes, for the development of a universal vaccine for a genetically heterogeneous human population [17, 27, 202-205]. In an attempt to develop a universal T cell epitope-based vaccine, and since CD8^{+} T cells appear to be crucial effectors of protective immunity against HSV-1 and HSV-2 infections [14, 24, 25, 27, 43-54], past-decade research from our laboratory has focused on two strategies: (1) identifying HLA-restricted epitopes on herpes protein antigens that are strongly recognized by human CD8^{+} T cell from seropositive "asymptomatic" individuals; and (2) immunization of "humanized" HLA transgenic animal models (mice and rabbits) with antigenic epitopes to determine their immunogenicity and protective efficacy against ocular and genital herpes infection and disease. In our ongoing prophylactic and therapeutic herpes vaccine program, we have already successfully identified several "symptomatic" and "asymptomatic" CD8^{+} T cell epitopes and have demonstrated pathogenic vs. protective efficacy in "humanized" HLA-A*0201 transgenic animal models [24, 43, 44, 158]. However, although the HLA-A*02 allele is frequent in three major population groups (i.e. in over 50% of Caucasoid, Hispanic and Oriental individuals), it is represented in the African ethnic groups in only 30% of individuals. Therefore, a universal herpes vaccine that provides a perfect coverage of human

population, regardless of race and ethnicity, should include multiple T-cell epitopes restricted by common HLA-A, HLA-B and HLA-C alleles worldwide, not just the HLA-A*0201 allele. A combination of nine HLA supertypes of cumulative high frequencies has been defined to provide an almost perfect coverage (greater than 99%) of the entire repertoire of HLA molecules [206]. Since a mixture of multiple epitopes is likely to stimulate polyclonal T-cell lines (one T cell clone for each epitope) and more effector T cells than a single epitope [26], we used multiple CD8^{+} T cell epitopes to induce a broader T cell response [26, 27]. Therefore, for a better coverage of all ethnic groups it is imperative to extend the discovery process and identify epitopes that are restricted to other HLA-A, HLA-B and HLA-C alleles, by selecting the HLA molecules with high cumulative frequencies in human populations around the world.

A universal herpes vaccine that is based on T cell epitopes presented by most common HLA-A, HLA-B, and HLA-C alleles of cumulative high frequencies in the four major world's populations (i.e. Caucasoids, Orientals, Hispanics and Blacks) would allow full coverage of the world population and thus a superior clinical response. Additionally, a therapeutic vaccine that would control the disease (in contrast to a prophylactic vaccine that prevent transmission) would be relatively more feasible and the results would be more testable, requiring a much smaller sample size. This is especially true in sub-Saharan regions where the prevalence of genital herpes disease remains high (e.g., in Kenya were greater than 50% are infected by genital herpes).

Towards this goal, our first step in driving a protective cellular immunity is the discovery of "protective" HLA-A, HLA-B, and HLA-C-restricted epitopes that are: (1) presented by common and highly frequent alleles that are cumulatively distributed throughout the 5 continents, regardless of race and ethnicity, making those T cell epitopes "universal" candidates to be included in a universal vaccine. For instance, because of the high frequency of the HLA-C*07, HLA-A*24, HLA-B*35 alleles of the five continents, epitopes restricted to those three alleles would be a good candidates to be included in an universal vaccine for a genetically heterogeneous human population [17, 27, 202-205]; (2) include "asymptomatic" presented by HLA-A, HLA-B, and HLA-C alleles that are mostly represented in non-endemic areas, because those alleles, and associated epitopes, might be involved in resistance to HSV infection and/or to a slow progression to herpetic disease. For instance, HLA-B*44 high expression and frequency that appears to positively correlate with low prevalence of HSV-2 infection known in Caucasoid European population (Fig. 2), makes HLA-B*44-restricted epitopes "good" candidates to be included in future herpes vaccine, and finally; (3) to exclude the "symptomatic" epitopes that are associated with HLA-A, HLA-B, and HLA-C alleles most represented in endemic areas, because those HLA-A, HLA-B, and HLA-C alleles and associated epitopes might actually be involved in susceptibility to HSV infection and may facilitate progression to herpetic disease. For instance, because HLA-A*24 is the most frequent allele of the HLA-A locus in sub-Saharan populations, where one of the highest prevalence of genital HSV-2 infection is recorded (Fig. 2), it makes HLA-A*24-restricted epitopes undesirable candidates to be included in future herpes vaccine candidates because these epitopes may actually be involved in the mechanisms that facilitate herpes infection and/or in the immuno-pathological mechanisms that exacerbate herpes disease.

The repertoire of epitope peptides presented by HLA class I molecules is largely determined by the affinity that is dictated by the structure of the peptide itself and of the HLA binding groove. It is expected that the molecules having similar grooves (i.e., belonging to the same supertype) might present similar/overlapping peptides. While T cell responses are detected against epitopes presented by alternative molecules across HLA class I supertypes and loci, peptide elution studies report minute overlaps between the peptide repertoires of even related HLA molecules. However, we should emphasize that different HLA class I molecules can nevertheless present largely overlapping epitope peptide sets, and that "functional" HLA polymorphism on the individual and population level is probably much lower than previously anticipated [207]. Thus, a recent study showed that an unexpectedly large fraction of epitopes (> 50%) appeared bind two or more HLA molecules, often across supertype or even loci [207]. It also appears from a most recent study that HLA class I alleles are associated with peptide-binding repertoires of different size, affinity, and Immunogenicity [208]. An in silico analysis of potential CD8^{+} T cell epitopes of consensus 84+ ORF sequences of HSV-1 and HSV-2 strains revealed relatively higher number of promiscuous epitopes in contrast to limited numbers of binders restricted by one haplotype at a time. This suggests that the extent of promiscuity of T cell epitopes of HSV restricted by HLA alleles exerting opposing effects might differ.

4. HLA-A*01:03, HLA-A*24:02, HLA-B*08:01, HLA-B*27:05, HLA-B*35:01, HLA-B*44:02 and HLA-C*07:01 transgenic mice: novel versatile pre-clinical models to determine the role of HLA class I in susceptibility/resistance to herpes infection and disease

There a lack of "humanized" small animal models to study the role of HLA alleles and their restricted epitopes in protection vs. susceptibility to HSV-1/HSV-2 infection and disease. HLA transgenic mice represent a suitable versatile small animal model system to quickly evaluate T cell responses specific to human epitopes and complex pathogens, such HSV-1 and HSV-2. To facilitate the design of an effective HLA-restricted epitope-based herpes vaccine, several HLA-A, HLA-B, and HLA-C monochain transgenic/H-2 class I null mice have been recently developed [158].

The second step in driving cellular protective immunity against herpes is the *in vivo* immunogenicity study and protective efficacy of naturally presented human CD8^{+} T cell epitopes in reliable HLA transgenic (Tg) animal models [14]. In our ongoing HSV therapeutic vaccine program, we have successfully used HLA-A*0201 Tg mice to determine the immunogenicity and protective efficacy of many human HSV-1 and HSV-2 epitopes [24, 43, 44]. However, for a full coverage of the world's European, African, Asian and Hispanic populations it is imperative to determine the immunogenicity of human epitopes that are restricted to other HLA class I (A, B and C) haplotypes that are highly represented in the populations where herpes is endemic [61]. We are currently mapping herpes epitopes restricted to other HLA class I and, in particular we are studying the immunogenicity protective efficacy of herpes epitopes in recently developed HLA-A*01:03, HLA-A*24:02, HLA-B*08:01, HLA-B*27:05, HLA-B*35:01, HLA-B*44:02 and HLA-C*07:01 mono-chain transgenic/H-2 class I null mice. The above set of HLA class I mono-chain transgenic mice combined with the already available HLA-A*02:01 and HLA-B*07:02 transgenic, *H-2*

KO mice [209, 210] would represent a large coverage of the four major world's populations (European, African, Asian and Hispanic) as detailed below:

α) HLA-A—As discussed above, the HLA-A*01 appears to be frequent in regions with high endemic herpes, such as sub-Saharan Africa. HLA-A*01:03 monochain transgenic/H-2 class I null mice, now available, will be used to study susceptibility/resistance to herpes infection and disease [158]. In addition, the immunogenicity and protective efficacy of herpes epitopes restricted to the HLA-A*01:03 molecule can be studied in HLA-A*01:03 transgenic mice [158]. While HLA-A*24 is the most frequent allele of the HLA-A locus in population with the highest prevalence of genital HSV-2 infection [85, 86], the question remains whether HLA-A*24 allele constitutes a resistance or susceptible factor for HSV-2 infection. Thus, the HLA*A24:02 monochain transgenic/H-2 class I null mice which we recently developed could also be used to determine whether they are more susceptible to HSV-1 and HSV-2 infection and disease as compared to their age- and sex-matched wild type mice counterparts. HLA-A*24:02 transgenic mice can also be used to determine whether HLA class I-mediated susceptibility to HSV-2 is associated with HLA-A*24 and to study the immunogenicity of potential "asymptomatic" herpes epitopes restricted to HLA-A*24:02 [158].

β) HLA-B—The HLA-B*08 allele is also highly represented in sub-Saharan populations which have the highest rates of HSV-1 and HSV-2 infections. HLA-B*08:01 monochain transgenic/H-2 class I null mice will be used to study whether these mice are more susceptible to HSV-1 and HSV-2 infection and disease [158]. In addition, the patho-immunogenicity of potential "symptomatic" herpes epitopes restricted to HLA-B*08:01 molecule can be studies in these new mice [158]. The question also remains whether this HLA-B*35 allele constitutes a resistance or a susceptible factor to HSV-1 and HSV-2 infection. HLA-B*35:01 monochain transgenic/H-2 class I null mice are also now available to study the immunogenicity of herpes epitopes restricted to HLA-B*35 haplotype [158]. It will be of interest to determine whether HLA-B*35:01 transgenic mice will resist herpes infection and disease compared to HLA-A*24:02 monochain transgenic/H-2 class I null mice. We expect HLA-B*35:01 transgenic mice to be resistant to infection while HLA-A*24:02 transgenic mice to be susceptible to infection.

A study comparing HLA frequencies among seronegative, HSV-2 seropositive asymptomatic individuals to HSV-2 seropositive symptomatic individuals appears to show association of HLA-B*27 with an increase in symptomatic herpes disease [56]. HLA B*27 is the only allele reported as associated to exacerbation of recurrence of ocular herpetic eye disease [57]. Since HLA-B*27:05 monochain transgenic/H-2 class I null mice are now available, it would be interesting to see whether these mice will be more susceptible or more resistant to genital and ocular herpes infection and disease.

The HLA-B*44 is so far the most frequent allele of the HLA-B locus in Caucasoid European population but not in sub-Saharan African nations where the prevalence of HSV-2 infection in highest (Fig. 2). Thus, HLA-B*44 allele may constitute a direct or indirect factor in resistance to HSV-2 infection. HLA-B*44:02 monochain transgenic/H-2 class I null mice, now available, will be used to determine whether they will be more resistant to herpes

compared to their wild type. It will also be of interest to determine whether HLA-B*44 transgenic mice will resists herpes infection compared to HLA-A*24:02 monochain transgenic/H-2 class I null mice. We expect HLA-B*44 transgenic mice to be resistant to infection while HLA-A*24:02 transgenic mice to be susceptible to infection. HLA-B*44:02 mice will also be used to study the immunogenicity and protective efficacy of herpes epitopes restricted to HLA-B*44 molecule [158].

γ) HLA-C—Although HLA-C*07 is the most frequent allele in the four major world's populations (Caucasoid, Hispanics, Orientals and Blacks), its association with resistance vs. susceptibility to herpes is unclear. The recently available HLA-C*07:01 monochain transgenic/H-2 class I null will be used to determine whether HLA-C*07 allele will lead to resistance or susceptibility to herpes infection and disease compared to wild type mice and to HLA-A*24:02 mice.

5. Concluding Remarks

Several points could be made from the above analysis:

- While the present study is focused on determining the association of HLA alleles with the prevalence of HSV-2 infections and disease; we do not ignore that other genetic, environmental, and socio-economic factors might also be involved in shaping up the prevalence of HSV-2 infections and diseases. For instance, while the high prevalence of herpes recorded in Sub-Saharan African populations is associated with high frequency of certain HLA alleles, it might also be affected by other co-infections, such as HIV, malaria and tuberculosis, that are also endemic in those regions. Nevertheless, HIV is far too recent to have exerted a pressing on the frequency of HLA alleles and on the prevalence of herpes. Moreover, malaria is geographically limited in its scope while tuberculosis is also typically limited to urban settings.

- The subset of "risk" HLA class I alleles that appears more strongly and consistently associated with high prevalence of herpes infections and diseases, i.e. "susceptibility" included HLA-A*24, HLA-B*27, HLA-B*53 and HLA-B*58 (Fig. 2 and Table 2B). We are evaluating whether HLA-B*27:05 monochain transgenic/H-2 class I null mice, recently developed, will be more susceptible to ocular herpes infection and disease

- High frequency of HLA-B*44 "protective" allele appears to be more strongly and consistently associated with low prevalence of herpes infections and diseases. (Fig. 2 and Table 2A). This makes HLA-B*44-restricted epitopes "good" candidates to be included in future herpes vaccine. We are also evaluating whether HLA-B*44 monochain transgenic/H-2 class I null mice, recently developed, will be more resistant to ocular herpes infection and disease.

- HLA-B5, HLA B*27 and HLA-A*30 are the only alleles reported as associated to exacerbation of recurrences of ocular herpetic eye disease [57]. We are in the process of evaluation whether HLA-B*27:05 monochain transgenic/H-2 class I null

mice, recently developed, will be more susceptible to ocular herpes infection and disease.

- The HLA B*27 allele is so far the only allele that is positively associated with exacerbation of ocular herpes disease and with high prevalence of genital herpes infection.

- Because of the high frequency of the HLA-C*07, HLA-A*24, HLA-B*35 alleles of the five continents, epitopes restricted to those three alleles would be a good candidates to be included in an universal vaccine for a genetically heterogeneous human population.

- Because HLA-A*24 is the most frequent allele of the HLA-A locus in populations where one of the highest prevalence of genital HSV-2 infection is recorded, it makes HLA-A*24 -restricted epitopes undesirable candidates to be included in a future herpes vaccine because these epitopes may be involved in an immune mechanism that increase herpes infection and/or exacerbates herpes disease.

- The findings in this report are a pure HLA-herpes-infection-disease associations and do not exclude other implications and immunogenetic factors that can affect the prevalence of HSV-2 infections and the resistance/susceptibility to herpes. Therefore, it would be of interest to further explore the influence of the genetic make-up of HSV-infected symptomatic vs. asymptomatic individuals. Comparing the immunogenetic profile of symptomatic vs. asymptomatic individuals might give clues for the individual course of the HSV infection and disease and will possibly lead to tailored therapeutic strategies in HSV-infected persons. Furthermore, sociologic factors such as sexual promiscuity and other high-risk sexual behaviors are likely to be associated with susceptibility to herpes infection but their role is beyond the scope of this review.

- The associations of certain HLA alleles with susceptibility or resistance to HSV-1 and HSV-2 infection may help develop effective epitope-based vaccine against herpes infection and disease. However, the above analysis on the association of the frequency of HLA class I alleles with the prevalence of herpes infection does not imply to exclude a linkage between HLA class II (HLA-DR, HLA-DP and HLA-DQ) alleles and resistance/susceptibility to herpes infection and disease.

- The present data constitute an association (rather than a cause or effect) and there may or may not be a direct relationship between an HLA haplotype and resistance/susceptibility to herpes. To directly assess whether HLA class I haplotypes play a role in susceptibility/resistance to herpes simplex virus infection and disease we have recently generated HLA-A*01:03, HLA-A*24:02, HLA-B*08:01, HLA-B*27:05, HLA-B*35:01, HLA-B*44:02 and HLA-C*07:01 monochain transgenic / H-2 Class I null mice. These novel, versatile pre-clinical mouse models of human T cell responses will also help us identify human epitopes restricted to specific HLA haplotype from the 84+ herpes proteins and assess the role of these epitopes in protection against genital and ocular herpes. The development of an effective vaccine against herpes is badly needed and would present an unparalleled

economical alternative for herpes control, as it provide the most cost-effective and safe means to reduce the estimated yearly toll of 400 000 ocular herpes and 200,000 to 500,000 cases of genital herpes reported so far in the US [101, 211-219]. These numbers should be viewed cautiously, because many herpes infections are not reported, many are not easily diagnosed, and many are asymptomatic or inapparent.

Acknowledgments

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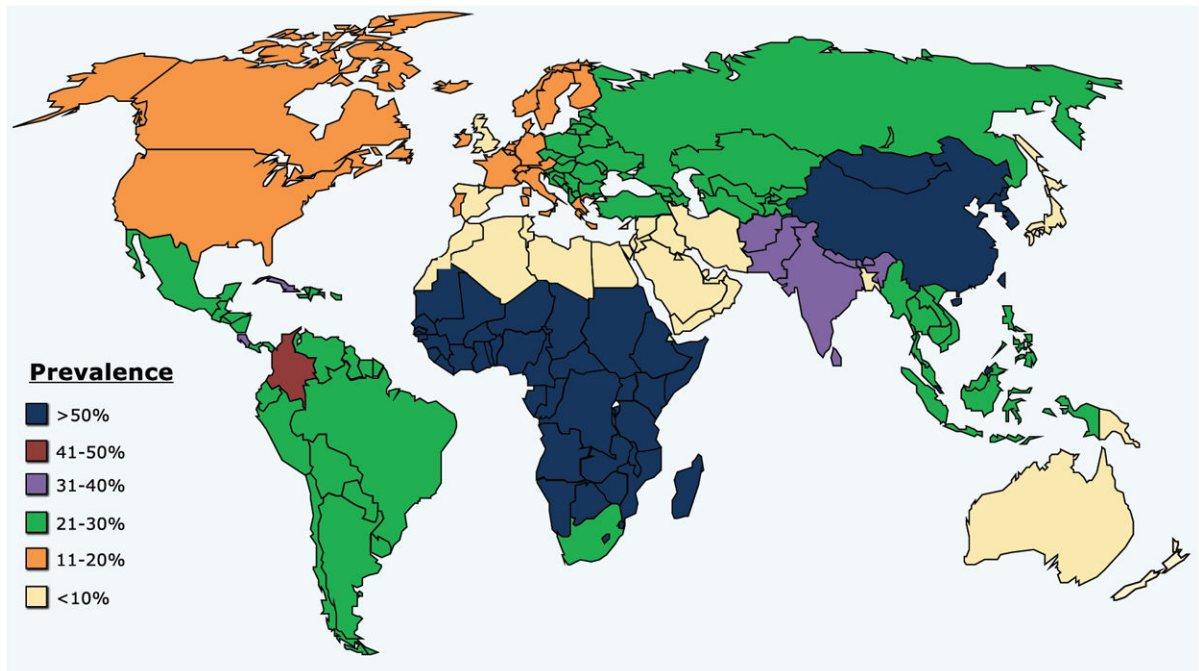
Figure 1.
The HSV-2 prevalence is generalized by world major regions, including Asia, Australia, Europe, Middle East, North Africa, North America, South/Central America and sub-Saharan Africa. HSV-2 prevalence per region was predicted based on representative populations within that region.
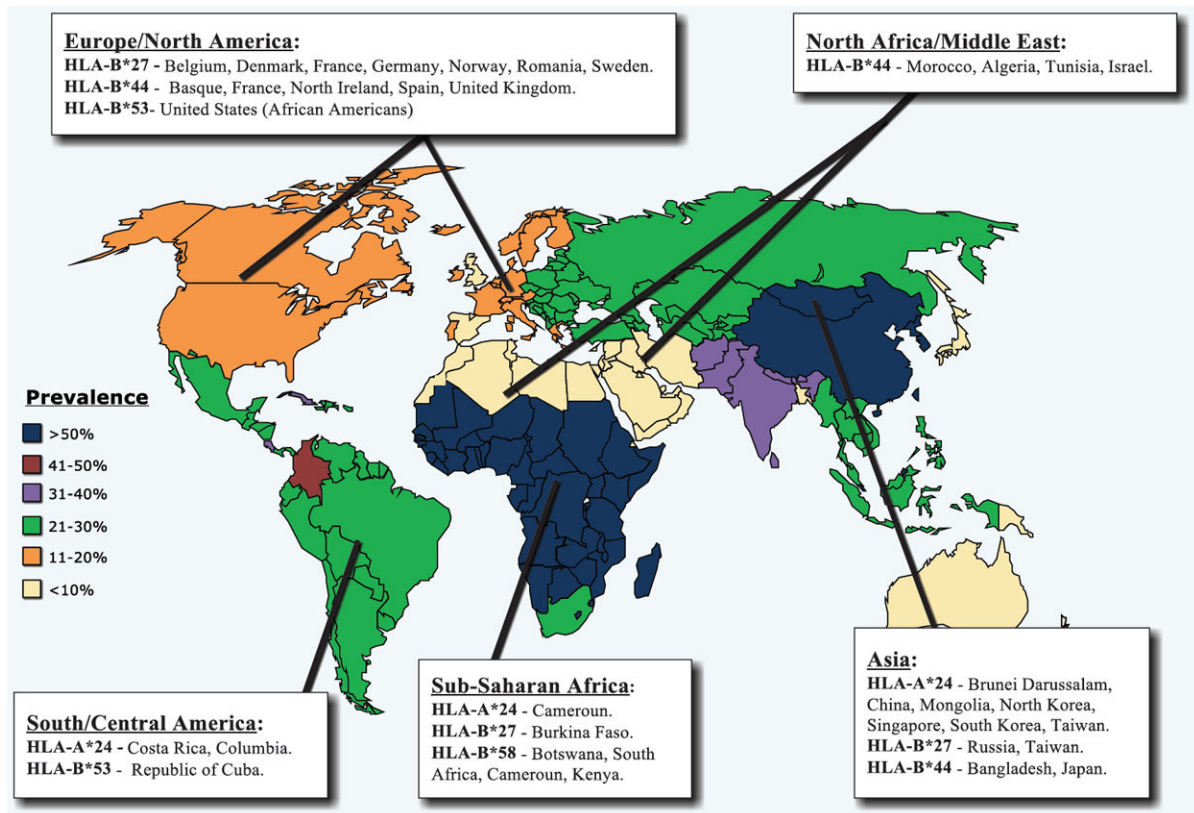
Figure 2.
High frequency of HLA-B*44 allele is reported in regions and ethnicities with low to moderate HSV-2 prevalence. High frequency of HLA-B*27 allele frequency is reported in regions and ethnicities with moderate to high HSV-2 prevalence. High frequencies of HLA-A*24, HLA-B*27, HLA-B*53 and HLA-B*58 alleles are only reported in regions and ethnicities with high prevalences.

Table 1

Prevalence of HSV-2 infection.

| Region	Sub-region [1]	Prevalence of HSV-2 Infection
Asia	Bangladesh, Brunei Darussalam, China, Japan, Mongolia, North Korea, Russia, Singapore, South Korea	Variable by Sub-regions
Australia	-	Low
Europe	Basque, Belgium, Corsica, Denmark, France, Germany, Northern Ireland, Norway, Poland, Republic of Ireland, Romania, Scotland, Spain, Sweden, United Kingdom,	Low
Middle East	Arab Nations, Iran, Israel	Low
North Africa	Algeria, Morocco, Tunisia	Low
North America	United States	Variable by Ethnic groups
South/Central America	Colombia, Costa Rica, Cuba	High
Sub-Saharan Africa	Botswana, Burkina Faso, Cameroon, Central African Republic, Ethiopia, Guinea, Guinea Bissau, Kenya, Mali, Natal Zulu, Rwanda, Senegal, South Africa, Uganda, Zambia, Zimbabwe	High

[1] Sub-regions listed are specifically referenced in the text

Table 2

A: Association of high frequency of HLA-B*44 allele with low/moderate prevalence of HSV-2 infection in various regions of the world.

	Sub regions	Prevalence of HSV-2 infection	HLA-B*44 allele frequency [1]
Asia	Bangladesh	Low	High
	Japan	Low	High
Europe	Basque	Low	Most frequent HLA-B (Caucasoid)
	France	Low	Most frequent HLA-B
	North Ireland	Low	35.7%
	Spain	Low (3.9% men genital herpes)	Most frequent HLA-B
	United Kingdom	Low (4% England)	32%
Middle East	Israel	Low	High
North Africa	Algeria	Low	High
	Morocco	Low	High
	Tunisia	Low	High
Sub-Saharan Africa	Cameroon	55% women, 36% men	Low
	Kenya	55% women, 36% men	Low
	South Africa	High	Low

B: Association of high frequency of HLA-A*24, HLA-B*27, HLA-B*53, and HLA-B*58 alleles with moderate/high prevalence of HSV-2 infection in various regions of the world.

	Sub regions	HSV-2 infection prevalence	HLA-A*24 allele frequency [1]	HLA-B*27 allele frequency [1]	HLA-B*53 allele frequency [1]	HLA-B*58 allele frequency [1]
	Oriental Asia	Low	-	-	<3%	-
	Bangladesh	Low (7% women genital herpes)	-	-	-	Low
	Japan	Low	-	0.1-0.5%	-	Low
	Russia	21-30%	-	10.2%	-	-
Asia	Taiwan	High	48.9%	15%	-	-
	Brunei Darussalam	61.8% women and 47.8% men aged 15-49	Most frequent HLA-A	-	-	-
	China			2.9%	-	-
	Mongolia			<2%	-	-
	North Korea			<2%	-	-

B: Association of high frequency of HLA-A*24, HLA-B*27, HLA-B*53, and HLA-B*58 alleles with moderate/high prevalence of HSV-2 infection in various regions of the world.

Region	Sub regions	HSV-2 infection prevalence	HLA-A*24 allele frequency[1]	HLA-B*27 allele frequency[1]	HLA-B*53 allele frequency[1]	HLA-B*58 allele frequency[1]
	Singapore		-	-	-	-
	South Korea			<2%	-	-
Europe	Caucasoid Europe	Low	-	-	<3%	-
Europe	Belgium	Low	-	14.3%	-	-
Europe	Denmark	Low	-	24%	-	-
Europe	France	Low	-	12%	-	-
Europe	Germany	Low	-	13%	-	-
Europe	Norway	Low	-	24%	-	-
Europe	Romania	Low	-	11.2%	-	-
Europe	Spain (men)	3.9% genital herpes	-	-	-	Low
Europe	Sweden	Low	-	16%	-	-
Europe	United Kingdom	Low	Low	8% (*27:05)	-	-
Middle East	Arab Nations	Low	-	low	-	Low
Middle East	Israel	Low	-	low	-	Low
North Africa	Morocco	Low	-	4%	<3% (Caucasoid)	-
North Africa	Algeria	Low	-	4%	<3% (Caucasoid)	-
North Africa	Tunisia	Low	-	4%	<3% (Caucasoid)	-
North Africa	Lybia	Low	-	4%	<3% (Caucasoid)	-
North Africa	Egypt	Low	-	4%	<3% (Caucasoid)	-
North America	United States (African Americans)	High	-	3%	25.5%, most frequent HLA-B	-
North America	United States (Caucasoid)	Low	-	-	<3%	-
South/Central America	South/Central America	Moderate	-	< 2%	-	-
South/Central America	Costa Rica	39% genital herpes women	2nd most frequent HLA-A	-	-	-
South/Central America	Columbia (Black, Mestizo)	50% women	Most frequent HLA-A	-	-	-
South/Central America	Republic of Cuba	High	-	-	Most frequent HLA	-
Sub-Saharan Africa	sub-Saharan Africa (Blacks)	High	-	3%	-	2nd most frequent HLA
Sub-Saharan Africa	Botswana	High	-	-	-	17.9%

B: Association of high frequency of HLA-A*24, HLA-B*27, HLA-B*53, and HLA-B*58 alleles with moderate/high prevalence of HSV-2 infection in various regions of the world.

Sub regions	HSV-2 infection prevalence	HLA-A*24 allele frequency [1]	HLA-B*27 allele frequency [1]	HLA-B*53 allele frequency [1]	HLA-B*58 allele frequency [1]
South Africa	High	-	-	-	Most frequent HLA-B, 39%
Burkina Faso	High	-	Most frequent HLA	-	-
Cameroun	55% women, 36% men	3rd most frequent HLA-A	-	-	Most frequent HLA-B
Kenya		-	-	-	

[1] http://www.allelefrequencies.net

Table 3

HLA allele association with low/moderate or moderate/high prevalence of HSV-2 infection organized by region: HLA-A*24, HLA-B*27, HLA-B*44, HLA-B*53, HLA-B*58.

Region associated with HIGH allele frequency	Association of high frequency of HLA alleles with moderate/high HSV-2 prevalence	Association of high frequency of HLA alleles with low/moderate HSV-2 prevalence	HSV-2 Infection Prevalence
Asia	HLA-A*24 HLA-B*27	HLA-B*44	Variable by sub-region
Europe	HLA-B*27	HLA-B*44	Low/Moderate
Middle East	-	HLA-B*44	Low
North Africa	-	HLA-B*44	Low
South/Central America	HLA-A*24, HLA-B*53	-	High
Sub-Saharan Africa	HLA-A*24, HLA-B*27, HLA-B*58	-	High

Table 4

Summary of all HLA class I allele associations with prevalence of HSV-2 infection.

HLA allele	Association with HSV-2 infections and diseases	Regions associated with HIGH allele frequency
HLA-A*01	Unclear	Australia, Europe, Middle East, North Africa, sub-Saharan Africa
HLA-A*02	Unclear	Australia, Europe, North Africa, South/Central America, sub-Saharan Africa
HLA-A*24	Positive [1]	Asia, sub-Saharan Africa, South/Central America
HLA-B*07	Unclear	Europe, sub-Saharan Africa
HLA-B*08	Unclear	Sub-Saharan Africa
HLA-B*15	Unclear	Asia, North America, South/Central America, sub-Saharan Africa
HLA- B*27	Positive [1]	Asia, Europe, sub-Saharan Africa
HLA-B*35	Unclear	Asia, Europe, Middle East, North Africa, South/Central America
HLA-B*44	Negative [2]	Asia, Europe, Middle East, North Africa
HLA-B*53	Positive [1]	South/Central America
HLA-B*58	Positive [1]	Sub-Saharan Africa
HLA-C*02	Unclear	Europe, sub-Saharan Africa
HLA-C*07	Unclear	Europe, Middle East, North Africa, North America, South/Central America

[1] HLA allele association with HIGH prevalence of HSV-2 infection, i.e. "susceptibility"

[2] HLA allele association with LOW prevalence of HSV-2 infection, i.e. "resistance"