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Original Synthetic Report

The peopling of the Americas: a complex issue for Amerindian, Na-Dene, Aleut and Eskimo first inhabitants

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Abstract - ***Aim:*** To compare the Amerindians HLA allele frequencies with those of other First American Natives and also those of other worldwide populations in order to clarify the still unclear peopling of the Americas and the origins of Amerindians. ***Subjects and methods***: All possible HLA data already obtained about early Native American populations are used. Genetic distances and N-J dendrogram method are applied. ***Results and conclusions:*** Results and discussion have given to the following conclusions: 1) Pacific Ocean boat trips may have contributed to the HLA genetic American profile (or *vice versa*); 2) North West Canadian Athabaskans have had gene flow with close neighboring populations, Amerindians, Pacific Islanders including East Australians, and Siberians; 3) Amerindians entrance to America may have been different to that of Athabaskans, Aleuts and Eskimos; Amerindians may have been in their lands long before Athabaskans and Eskimos because they present and altogether different set of HLA-DRB1 allele frequencies; 4) Amerindians show very few "particular" single-locus alleles, but have unique extended haplotypes; 5) Our results do not support the three-wave model of American peopling, but another model where the Pacific Coast is also an entrance point. Reverse migration (America to Asia) is not discarded and different movements of people in either direction in different times are supported by the Athabaskan population admixture with Asian-Pacific population and with Amerindians.

Key words: Aleuts, Amerindians, Athabaskans, Eskimo, HLA, peopling of America.

Introduction

The First Amerindian are proposed to have come from Asia through the Bering land bridge between 30,000–10,000 years before the present (BP). These conclusions have been based on cultural, morphological and genetic similarities between American and Asian populations. Both Siberia (Crawford et al., 1998) and Mongolia (Kolman et al.,1996; Merriwether et al., 1996) have been put forward as the most likely places of origin in Asia.

Greenberg first postulated the triple migration theory for explaining the peopling of the Americas (Greenberg et al., 1986): Amerindians (12,000 years BP), Na-Dene (8,000 years BP) and Eskimo-Aleuts (6,000 years BP) (Fig. 1**)**; other authors postulate only one wave coming from Mongolia / North China as giving rise to the First Native American ancestors (Kolman et al., 1996; Merriwether et al., 1996).

mtDNA and Y Chr markers have been used to study the origins postulated time and place of entrance of Amerindians, Athabaskans and Eskimo (Goebel et al.,2008) into America. Also, archeological findings have been contrasted with genetic data (Crawford et al., 1998; Holden et al.,1999; Goebel., 2008). In the end, conclusions are diverse and no consensus exists about Amerindian origin and relatedness (Kolman et al., 1996; Merriwether et al., 1996; Goebel et al.,2008; Santos et al., 1999). We think the important issue is whether immigrants (Amerindians) were already differentiated (in Asia) into such ethnic groups whose descendants are still to be found in Asia. If they were differentiated then the question of how and when they crossed the Bering Land Bridge becomes secondary (Uinuk-Ool et al., 2002).

In this regard, HLA data may be more informative than Y Chr and mtDNA (Uinuk Ool et al., 2002) because maternal and paternal lineages and both frequencies (i.e.: genetic distances, dendrograms and correspondence analyses) and genealogies (specific HLA alleles and haplotypes) may be studied for comparing populations. The best evidence that HLA is a good genetic marker for studying population relatedness is that it usually correlates with geography.

Alu-insertion research yields results that are not concordant with the multiple-wave migration hypothesis (Novick et al., 1998). Results from this, and from other HTLV-1 virus strain investigations, led to the suggestion of a Trans-Pacific route of American peopling from Asia or Polynesia (Leon-S et al., 1996), which could have introduced some HLA alleles (Cerna et al., 1993; Holden et al., 1999). Finally, both genetic (Bruges-Armas et al., 1999) and archaeological (Holden et al., 1999) evidence suggests that a two-way Trans-Atlantic traffic occurred before Columbus discovered America (Fig. 1) (Holden et al., 1999).

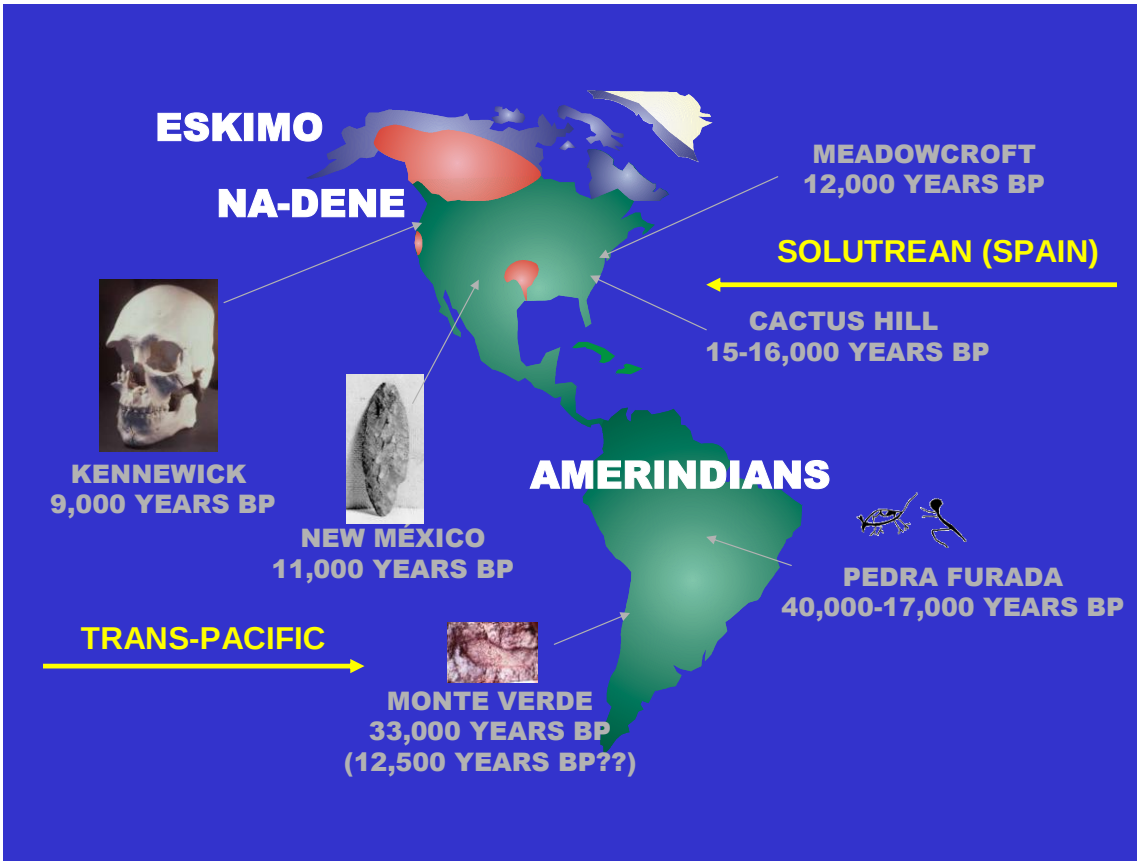

Figure 1 (Footnote): *It depicts the most popular theory of peopling of this continent from Asia though Bering Strait (Greenberg et al, 1986). Green: Amerindians (30,000-12,000 years BP); Red: Na-Dene (8,000 years BP), Athabaskans in Canada, Californian Indian isolates and Navajo and Apache from Southern United States; Blue: Eskimo (6,000 years BP). Aleuts from Aleutian Islands in Bering Strait are separate from Eskimo in linguistic and other anthropological parameters and were present in the Islands before Eskimos reached North America; in addition, Aleut HLA profile is different from Eskimo profile (Moscoso et al., 2008). Other theories of peopling of Americas (Yellow arrows): Trans-Pacific (from Australia-Pacific Islands (Cerna et al., 1993)), and from Iberian Peninsula Solutrean people (Bruges-Armas et al., 1999; Holden et al. 1999). Archeological relevant findings are also represented (Holden et al. 1999). Kennewick man from Washington State, USA; Meadowcroft (Pensylvania, USA); Cactus Hill (Virginia, USA); Pedra Furada (Brasil); Monte Verde (Chile).*

All these discrepancies and uncertainties about Amerindian origins may be due to methodological errors. For instance, functional molecules, cytochrome (cyt) b mtDNA, are erroneously used against an admixture of intronic and exonic DNA markers, as in the Alu or STR studies. Besides, population movements should be studied as movement of groups of genes, i.e.: with gene frequencies (genetic distances, dendrograms and correspondence analyses), which better reflect a population displacement and other populations (Asian / Amerindian) relatedness, and afterwards completed with genealogies (quasi-specific HLA alleles, HLA haplotypes, mtDNA and Y Chr markers). Genetic studies with an admixture of most available markers and other data have not clarified the Americas peopling yet (Goebel et al. 2008; Mulligan et al. 2008).

Materials and Methods

Thus, in the present work, we have studied the North, Meso and South American Amerindians' HLA gene frequencies and compared them with those of other North American Indians and worldwide populations, particularly with Asian and Pacific populations. Also, we have studied the following Amerindian ethnic groups: Seri, Mixe, Mixtecans, Zapotecans, Guaranis (Petzl-Erler et al., 1997), Lakota Sioux (Leffell et al., 2004), Mazatecans (Arnaiz-Villena et al., 2000), Teeneks (Vargas-Alarcon et al., 2006), Mayans (Gomez-Casado et al., 2003), Kogi, Arsario, Arhuacs, Wayu (Yunis et al., 1994), Cayapa (Titus-Trachtenberg et al., 1994) Lamas (Moscoso et al., 2006), Aymaras (Arnaiz-Villena et al., 2005) Quechuans (Martinez-Laso et al., 2006), Terena Indians (Lazaro et al., 1999), Xavantes, Mayos (Arnaiz-Villena et al., 2007), Uros (Arnaiz-Villena et al., 2009), Nahuas (Vargas-Alarcon et al., 2007), Tarahumaras (Garcia-Ortiz et al., 2006), Toba Pilaga, Mataco Wichi, Eastern Toba (Cerna et al., 1993), Mexican Mestizos and Jaidukama (unpublished results) and also Aleuts (Moscoso et al., 2008). A total of 14,698 chromosomes were analyzed.

Our aims are: - *Genealogy comparisons.* To determine the HLA class I (A and B) and class II (DRB1 and DQB1) highly specific Amerindian allelic lineages (hereafter ''alleles'' for simplicity) or specific HLA haplotypes by using DNA sequencing and serology; in other words, the most frequent HLA alleles and haplotypes in Amerindians which do not exist or exist in very low frequency in other populations.

- *Gene Group comparisons.* To compare the Amerindians HLA allele frequencies with those of other First American Natives (Na-Dene, Eskimo and Aleuts) and also those of other worldwide populations in order to clarify the still unclear peopling of the Americas and the origins of Amerindians.

Results and Discussion

HLA-DRB1 genes and HLA haplotypes in the Americas

We have chosen DRB1 alleles because many populations are typed for DRB1 high resolution alleles and very few for HLA class I or other class II loci. The low number of class I alleles found may be artificial, since many of them may not have been yet detected.

Meso and South American DRB1 Amerindian alleles are almost specific; alleles DRB1*0411 and DRB1*0417 were found only in all studied Meso and South Amerindians.

On the contrary, North American alleles are clearly shared with other non-Amerindian (Asian/ Pacific) populations (not shown). This is concordant with the existence of gene flow between Amerindians and Pacific or Siberian people, but not necessarily with a migration of Amerindians from Asia or Pacific Areas, although there are signs of cultural or genetic contacts with Asia or even with Iberians (Holden et al., 1999; Bruges-Armas et al., 1999) (Fig. 1). DRB1*0802 is present in almost all Amerindians, and also in Siberian Eskimos and Japanese Ainu. DRB1*0407 is present in almost all Amerindian populations and absent or in a non-significant frequency in other populations. DRB1*0403 is present in one of South American most frequent haplotypes but is also frequently found throughout Pacific Islands (Samoa, Papua New Guinea, New Zealand Maori, Taiwan, Tonga, Cook Islands) (Middleton et al., 2009). A Pacific gene flow in either direction may not be discarded by this genealogy approach also.

Extended HLA haplotypes in America: genealogy analysis. Correspondence and NJ multidimensional relatedness with other populations: HLA allele frequency in population analysis.

- North-Americans. The most frequent extended haplotypes in North Americans are specific for North American populations, Yupik (Eskimos), and Aleuts, and one of the most frequent haplotypes is also found in Taiwan and Japanese populations (A*24-B*40-DRB1*1401-DQB1*0503). This shows that a low degree of North American haplotype sharing is found between North American and Asian-Pacific populations. However, there is a clear genetic HLA relatedness between isolated populations close to Beringia: Eskimos, Udegeys, Nivkhs (North East coast of Siberia) and Koryaks and Chukchi from extreme North East Siberia (Fig. 2), and North West American populations: Athabaskan, Alaskan Eskimos (Yupik) and Tlingit.

These results suggest that admixture occurred between extreme North East Siberian groups and North American Na-Dene (including Tlingit) and Eskimo (Yupik) people, but do not tell us whether migrations in both directions occurred.

On the other hand, Asian populations which are geographically not close to Beringia (Japanese, Ainu, Manchu, Singapore Chinese, Buyi) do not cluster with North Americans neither in NJ dendrogram (Fig. 2) or correspondence analysis (not shown).

Finally, Lakota-Sioux Amerindians which have inhabited in North United States, are not related with Asians and West Siberians (Fig. 2) but with Meso and South Americans.

- Meso-Americans. Most frequent haplotypes (not shown), relatedness dendrograms (Fig. 2) and correspondence (not shown) do not relate these Amerindians with any Asian population, including North East Siberians. Haplotypes of Meso-Americans are shared with other Amerindians and one of them with Alaskan Eskimo (Yupik): A*02-B*35-*DRB1*0802-DQB1*0402.

- South-Americans. These Amerindian speaking groups are related to other South-American Amerindians and to Meso-American Amerindians (Fig. 2). Most frequent haplotypes are shared with other American Amerindians, but not with Asians.

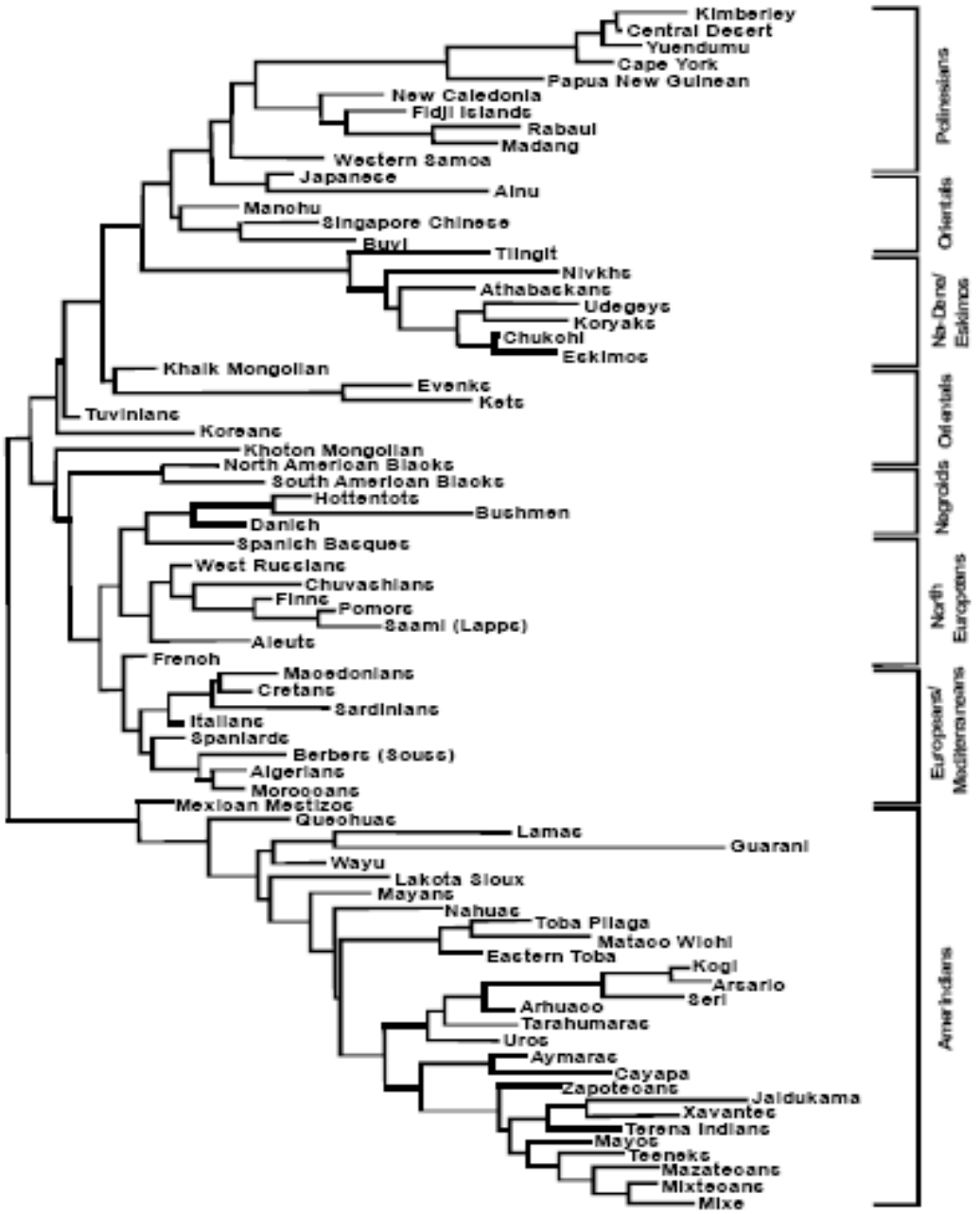

Figure 2

(Footnote): *Neighbor-Joining dendrogram obtained by using HLA-DRB1 allele frequencies. The genetic relatedness among Amerindians, Na-Dene, Eskimos, Asians, Negroids, Europeans and Polynesians are determined by calculating the genetic distances between populations (DA), using HLA-DRB1 allele frequencies. Amerindians cluster together and separated from the rest of the world populations (Arnaiz-Villena et al., 2007; Arnaiz-Villena et al., 2009; Garcia-Ortiz et al.,2006 ; Moscoso et al., 2008) .*

In summary, Amerindians have little relatedness with Asians, according to genealogy studies. North-Americans only share one haplotype (A*24-B*40-DRB1*1401-DQB1*0503) with Taiwanese and Japanese in low frequencies.

Specific extended haplotypes for Amerindian ethnic groups and Aleuts

Some new extended 4-loci haplotypes have been found only in Amerindian and Aleut specific groups and in no other Amerindian or World population (Table 1).

New specific haplotypes are found in North and South Amerindians, while specific alleles for a particular Amerindian population are rarely found or not found. This is concordant with the fact that HLA haplotype frequencies show greater variation among racial groups than individual loci (Bodmer et al., 1978). Thus, new allele appearance must be a relatively rare event (usually by gene conversion (Martinez-Laso et al., 2004)). Selection for variability within North and South American Natives is acting upon haplotypes more than upon alleles. This finding may be universal for all World populations.

Table 1: Extended haplotypes found only in some Amerindian populations (Arnaiz-Villena et al., 2000; Arnaiz-Villena et al., 2007; Gomez-Casado et al., 2003; Martinez-Laso et al., 2006; Moscoso et al., 2006; Moscoso et al., 2008; Vargas-Alarcon et al., 2007).

HAPLOTYPE				(freq. %)	POPULATION
A	B	DRB1	DQB1		
02	39	1602	0301	3.3	Mazatecans
02	62	1602	0301	3.3	Mazatecans
02	15	0404	0302	1.5	Mayans
02	39	0802	0402	3.4	Aymaras
02	39	0901	0303	3.4	Aymaras
02	48	0403	0302	7.8	Lamas
02	48	0804	0402	7.8	Lamas
02	39	1402	0301	3.6	Lamas
66	41	1303	0301	3.6	Lamas
02	48	0411	0302	2.4	Lamas
24	15	0901	0303	1.8	Lamas
33	38	1104	0301	1.8	Lamas
68	35	0802	0402	3.6	Quechua
02	48	1402	0301	2.9	Quechua
02	48	0802	0402	2.2	Quechua
02	52	0411	0302	3.7	Teeneks
68	35	1402	0301	2.8	Teeneks
68	40	1602	0301	2.6	Teeneks
68	35	1406	0301	2.6	Teeneks
02	35	1406	0301	4.2	Mayos
02	48	0404	0302	3.3	Mayos
24	51	0407	0302	3.3	Mayos
02	08	0407	0302	2.5	Mayos
30	49	1001	0501	7.5	Nahuas
02	52	1402	0301	2.7	Nahuas
68	61	1602	0303	2.0	Nahuas
24	15	1402	0301	3.2	Uros
68	35	0404	0302	3.2	Uros
24	48	0403	0302	2.2	Uros
02	40	0101	0501	5.6	Aleuts
24	37	0801	0402	4.2	Aleuts
24	39	0404	0302	4.2	Aleuts
24	39	1201	0301	4.2	Aleuts
02	15	0401	0301	2.8	Aleuts
02	51	1501	0602	2.8	Aleuts
26	40	1401	0503	2.8	Aleuts
32	44	0701	02	2.8	Aleuts
68	40	0404	0302	2.8	Aleuts
68	40	0802	0402	2.8	Aleuts
68	39	1201	0301	2.8	Aleuts

Languages do not correlated with genes

Some authors find correlation between genes and languages when selected ethnic groups and selected languages are used but only at macrogeographical level; however, Fig. (**2**) (NJ dendrogram) shows that the Na-Dene/Eskimo/Siberian group is genetically very close as measured by HLA-DRB1 frequencies and speak distant languages ; this is confirmed by HLA-DRB1 and HLA-DQB1 correspondence analysis (not shown). Both NJ and correspondence analysis correlate quite well with geography but not with languages. This is particularly evident in the Amerindian group where their genetic grouping (Fig. 2) do not correlated with their languages, i.e.: Mayans are close to Lakota-Sioux and Nahuas-Mexicas, whose languages are completely unrelated. Genes are inherited and languages have been imposed throughout history. Also, languages and genes evolution speed is different.

HLA in Amerindians shows gene flow with other Asian, Australian and Pacific Ocean inhabitants

HLA dendrograms or correspondence analyses based on HLA frequencies show that Amerindians (in the sense of Greenberg definition, (Greenberg et al., 1986)) seem to be separated from other worldwide populations, including northern Canadian Athabaskans and Eskimos. The latter cluster is in Figure 2 with Siberians. This means that HLA-DRB1 and HLA-DQB1 allele frequencies are completely different in Amerindians compared to other First American Natives or other World populations.

In addition, the studied populations show particular HLA 4-loci haplotypes for each specific studied population (Table 1). This is not the case for HLA-DRB1 alleles: except for two DRB1 alleles —DRB1*0411 and DRB1*0417—, Meso and South American Amerindians are shared with 1) Siberians, 2) other First American Inhabitants including Athabaskans and Eskimo, but not Aleuts (Moscoso et al., 2008), 3) Asian Pacific Coast populations (Ainu, Japanese, Taiwan) and to a lesser extent with Indochina people and, 4) East Australian Aborigines and Pacific Islands, like Papua New Guinea or Samoa groups.

A 2-loci (Moscoso et al., 2008), genealogy study, which completes our population frequency study, showed that Athabaskan DRB1-DQB1 genes are shared with: 1) neighbors, including Alaskan Eskimo (Yupik), 2) Amerindians from North and South America, 3) Siberians, 4) Pacific Islands inhabitants, and even Eastern Australia Aborigines. This suggests that Athabaskans are composed of a genetic HLA admixture and that gene flow has occurred between Athabaskans and all the other above mentioned Pacific-Asian populations. The hypothetical HLA gene flow may have occurred in different directions in different times. This shows that not only Beringia was an active pass of primitive Amerindians, but also Pacific navigation was.

Results on North American and South American population HLA alleles also support this view. Why nowadays Amerindian populations are altogether different to the rest of the World regarding HLA frequencies is only a matter of speculation: about 80 million early American Natives died during the XVI century (Dobbins, 1993), mainly due to a lack of appropriate immune response to European-borne diseases, mainly measles, influenza and plague (Dobbins, 1993) . This may have shaped the American Native HLA profile by increasing rare HLA alleles able to present new pathogens to T cells (Bodmer et al., 1978; Slade et al., 1992; Takahata et al., 1990). However, other early North American Natives (non-Amerindians) also suffered many epidemics (Dobbins, 1993) and do not have as different HLA profile from Asians, as Amerindians do.

Conclusions

- Canadian Athabaskans Indians have had gene flow with a) close neighboring populations, b) Amerindians, c) Pacific Islanders including East Australians and d) Siberians.
- Bering Strait was not probably the only entrance of people to Americas: Pacific Ocean boat trips may have contributed to the HLA genetic American profile (or the opposite could also be true).

- The Amerindian entrance to America may have been different to that of Athabaskans and Eskimos and Amerindians may have been in their lands long before Athabaskans and Eskimos because they present altogether different sets of HLA-DRB1 frequencies.

- Amerindians show very few "particular alleles"; almost all are shared with other Amerindians, Athabaskans, Pacific Islanders, including East Australians and Siberians. However, specific Amerindian extended haplotypes are found in isolates.

- Languages and genes evolve very differently.

- The three-wave model of American peopling is not supported by our data, but another model where the entrance is not only Beringia, but also the Pacific Coast. Reverse migration (America to Asia) is not discarded and different movements of people in either direction in different times are supported by the Athabaskan population admixture with Asian-Pacific population and with Amerindians.

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