Different Evolution of Inhibitory and Activating Killer Immunoglobulin Receptors (KIR) in Worldwide Human Populations

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Abstract: HLA class I molecules are ligands for natural killer cells' inhibitory (KIR DL) and activating (KIR DS) receptors. KIR DL receptors have a greater avidity for HLA class I molecules than KIR DS receptors. Thus, there is a possibility that HLA molecules drive KIR receptor selection.

We have used the percentage of individuals bearing the genes KIR 3DS1, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 2DL1, 2DL2, 2DL3, 2DL5 and 3DL1 in relatively well defined populations to test whether there is a different way of relating worldwide populations between KIR DS and KIR DL molecules.

We have used ARLEQUIN, DISPAN and VISTA computer programs to construct dendrograms and correspondence analyses showing the genetic relationships among different human world populations. Analyses based on KIR DS or KIR haplotype B genes show that populations are related according to geography, like a good anthropological marker (i.e.: HLA or Y chromosome systems). The results based on KIR DL or KIR haplotype A genes do not show such a correlation. Results are discussed taking into account the linkage of both HLA and KIR systems to microbial diseases and the possible evolutionary shaping of both HLA and KIR receptors repertoire by pathogens.

Keywords: Activating KIR, HLA, inhibitory KIR, populations.

INTRODUCTION

Natural killer cells play a pivotal role in innate immunity against viral infections [1] and in reproduction [2]. These functions are regulated by a number of receptor families. The most studied of these has been the killer Ig-like receptor (KIR) family. This group of receptors consists of at least 17 genes, two of which are pseudogenes. These receptors may either be inhibitory or activating. The KIR receptors can be divided into two haplotypes A and B. Whilst the A haplotype contains only one activating gene (KIR 2DS 4) which in many individuals is not expressed, the B haplotype has several activating genes [3].

Inhibitory KIR receptors specific for MHC (HLA in humans) class I molecules attack many viral infected cells without the specific class I surface ligand; the stronger the MHC ligand inhibition, the stronger the NK attacks [4-6]. In addition, it has been shown that certain activating KIR genes may have evolved under purifying selection, while other inhibitory KIR receptors encoded by alleles from the same locus (KIR 3DL1 / DS1) have been subjected to balancing selection (variability) [7]. This balancing selection may have been due to selective forces like a) the heterozygote advantage to cope with as many as possible infections or b) frequency dependent selections where the presence of many low frequency alleles may have a crucial role in saving a particular (human) population from new viruses.

Previously, we reported the frequency of the KIR genes and the allele frequencies of eight of these genes in seven diverse populations. At that time we compared the gene frequency results in these seven populations with results from those populations who had data available for 14 KIR genes (all KIR genes except 2DP1 and 3DP1 but no differentiation between KIR 2DL5A and KIR 2DL5B) available on the website http: //www.allelefrequencies.net (August 25th, 2008) [8]. Data from 56 populations was used but many of these populations could not be thought of as true in the anthropological sense [9].

In order to test whether KIR inhibitory receptors have underwent a different evolution compared to KIR activating receptors in world populations, we decided to extend our study to include only populations that would be subjected to the least apparent admixture because they are anthropologically well defined and living for a relative long time in a geographic stable area. Thus, in the present work, we aimed to compare the evolution of activating *versus* inhibitory NK receptors with geography.

MATERIAL AND METHODS

KIR Gene Percentages in Populations

The following genes were taken into account for the present analysis: for activating genes KIR 3DS 1, 2DS 1,

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2DS2, 2DS3, 2DS4, 2DS5 and for inhibitory genes 2DL1, 2DL2, 2DL3, 2DL5 and 3DL1. Every individual in the populations analysed was positive for KIR2DL4, KIR3DL2 and KIR3DL3, thus these genes were excluded from the analyses. In addition, separate analyses were performed according to whether the gene would be associated with the A haplotype or the B haplotype. For analysis of KIR haplotype B the following genes were included: 2DL2, 2DL5, 3DS1, 2DS1, 2DS2, 2DS3 and 2DS5. For KIR haplotype A the KIR genes 2DL1 and 2DL3 were included. The KIR genes 2DS4 and 3DL1 were not included in either haplotype as although more often found on KIR haplotype A they are present in 50% of KIR haplotype B [10]. Alleles were not taken into account as data is only available in a few populations (http://www.allelefrequencies.net; August 25th, 2008).

Populations Studied

The human populations quoted in Table **1** were investigated; all individuals were healthy and unrelated. Further details of these populations can be obtained by performing a search for KIR genes on the website and then clicking on the population name. The percentage of individuals carrying each KIR gene was calculated and gene frequencies compared to similar data in other populations which were on the website http://www.allelefrequencies.net (August 25th, 2008). These populations were chosen among others also on this website, because they were anthropologically quite well defined: i.e.: no big amount of admixture was supposed; also, most of them had a cultural definition. For example, the Buenos Aires (Argentina) sample is mostly built up by White European Caucasoid inhabitants. However, a caveat should be stated at this point that we are aware that we are working with a rough approximation, and results will be discussed on these bases. In addition, different methodologies have been used for KIR alleles detection in different laboratories.

Genetic and Statistical Analyses

Separate non-rooted dendrograms were constructed with gene frequencies of inhibitory KIR genes (DL) activating KIR genes (DS), genes on KIR haplotype A and genes on KIR haplotype B, using the Neighbour-Joining (NJ) method [11] with the genetic distances between populations (DA [12]) using DISPAN software comprising the programs GNKDST and TREEVIEW [13,14]. Correspondence analysis in n dimensions and its bidimensional representation was carried out using the VISTA V5.02 computer programme (http://forrest.psych.unc.edu) [15]. Bootstrap analysis is not useful when population samples analysed for allele frequencies comparisons are of a substantially different size, as in the present results occur.

RESULTS

Genetic Distances According to KIR Frequencies Variation

Amerindians are populations which have a very specific and distinct HLA profile from all other populations of the world [16,17]. We chose the isolated Tarahumara Amerindians from North Mexico [18] as the basal comparison ethnic group, a group which is sharply defined by both genetically and anthropologically criteria. Also, this Tarahumara group has been shown to have a comparatively low number of KIR genotypes [19].

Table 1. Populations Analysed in the Present Work. Names are Indicated as they Appear in the Website http://www.allelefrequencies.net (August 25th, 2008)

Population N		Ref.	Population	N	Ref.
Argentina Buenos Aires	365	[22]	Mexico Purepechas	53	[19]
Argentina Chiriguanos	54	[22]	Mexico Tarahumaras	65	[19]
China Zhejiang Han	104	[23]	Oman 9	9	[9]
Comoros 5	4	[24]	Pakistan Karachi	78	[25]
Cook Islands	48	[26]	Palestine Jordan	105	[27]
England 136		[27]	Samoa 5	0	[26]
Finland Helsinki	101	*	Senegal	90	[28]
France Southeast pop2	38	[24]	Singapore Chinese	47	[9]
France West	108	[28]	South Africa Xhosa	50	[9]
Guadaloupe 118		[28]	South Korea	154	[29]
Hong Kong Chinese	100	[9]	Spain Basque	71	[30]
India North Hindus	72	[31]	Sweden Vasterbotten	150	[32]
Ireland Northern pop2	154	[10]	Thailand Bangkok	119	[27]
Ivory Coast Abidjan	25	[33]	Tokelau 47		[26]
Japan 132		[34]	Tonga 49		[26]
Lebanon 120		[35]	Venezuela Bari	80	[36]
Macedonia 120		*	Venezuela Warao	89	[36]
Mexico City Mestizo	86	[19]	Venezuela Yucpa	61	[36]
Mexico Huicholes	73	[19]			

* Unpublished. Data taken directly from the website.

KIR DS genetic distances from Tarahumara to all other populations (Table **2**) show a trend to be concordant with a geographical / historical gradient. Roughly, the longer the genetic distance the longer the geographical / historical distance. The same phenomenon is shown for KIR haplotype B genes (Table **3**).

However, when KIR DL gene frequencies were analysed (Table **4**), there was no apparent correlation between genetic distances and populations' geography / history. Even Amerindians did not cluster together (see Bari, Wichi and Yucpa). This was also the case for KIR haplotype A genes (data not shown).

Also, a clear geographical gradient is shown in Tables **2** and **3** and their corresponding dendrograms and correspondence analyses in spite of the different technologies used in different laboratories.

NJ Dendrograms and Correspondence Analyses

The average differences in percentage of individuals in the populations having the analysed KIR genes is represented by the Neighbour-joining (NJ) dendrogram (Figs. **1**, **2**, **5**) and the correspondence analysis (Figs. **3**, **4**, **6**), based on the calculated DA genetic distances [12] and a value related to frequencies variance [15], respectively.

Table 2. DA Genetic Distances (x100) from Tarahumaras to Other Populations According to KIR DS Genes

Population D	A (x100)	Population D	A (x100)
Mexico Purepechas	0.38	France West	5.63
Venezuela Bari	0.98	Singapore Chinese	5.64
Argentina Chiriguanos	1.23	Oman	5.80
Mexico Huicholes	1.87	Macedonia	5.85
Venezuela Yucpa	3.00	Sweden Vasterbotten	6.14
Venezuela Warao	3.11	Tokelau	6.41
Mestizo City Mestizo	3.14	Lebanon	6.51
Finland Helsinki	3.15	Samoa	6.57
Spain Basque	4.16	France Southeast pop2	6.62
England 4.	30	Guadaloupe	6.74
South Korea	4.65	India North Hindus	6.75
Argentina Buenos Aires	4.68 P	alestine Jordan	7.01
China Zehjian Han	4.99	Comoros	7.24
Hong Kong Chinese	5.00	Pakistan Karachi	7.31
Ireland Northern pop2	5.19	Tonga	7.53
Thailand Bangkok	5.37	Ivory Coast Abidjan	10.40
Japan 5.	47	Senegal	10.60
Cook Islands	5.47	South Africa Xhosa	12.05

Table 3. DA Genetic Distances (x100) from Tarahumaras to Other Populations According to KIR Haplotype B Genes

Population D	A (x100)	Population D	A (x100)
Mexico Purepechas	0.30	Singapore Chinese	4.72
Venezuela Bari	0.80	Cook Islands	4.78
Argentina Chiriguanos	1.03	Tokelau	4.89
Mexico Huicholes	1.47	Sweden Vasterbotten	5.10
Finland Helsinki	2.48	Samoa	5.14
Mexico City Mestizo	2.59	Macedonia	5.17
Venezuela Warao	2.75	Japan	5.18
Venezuela Yucpa	3.16	France Southeast pop2	5.27
England 3.	45	Lebanon	5.32
Spain Basque	3.62	Guadeloupe	5.54
Hong Kong Chinese	4.06	Palestine Jordan	5.76
Argentina Buenos Aires	4.10	Comoros	5.77
Ireland Northern pop2	4.18	Tonga	5.94
Thailand Bangkok	4.24	Pakistan Karachi	6.30
South Korea	4.32	India North Hindus	6.59
Oman 4.	55	Senegal	8.36
China Zhejiang Han	4.61	Ivory Coast Abidjan	8.44
France West	4.62	South Africa Xhosa	10.19

Table 4. DA Genetic Distances (x100) from Tarahumaras to Other Populations According to KIR DL Genes

Population D	A (x100)	Population D	A (x100)
Mexico Purepechas	0.02	France West	1.92
Mexico Huicholes	0.13	Lebanon 2.	07
Mexico City Mestizo	0.39	England 2.	12
Finland Helsinki	0.79	Sweden Vasterbotten	2.15
Singapore Chinese	0.79	Tokelau 2.	41
Hong Kong Chinese	0.95	Guadaloupe 2.	45
Samoa 1.	02	Venezuela Warao	2.48
Thailand Bangkok	1.15	Argentina Buenos Aires	2.84
Comoros 1	.26	Macedonia 2.	98
France Southeast pop2	1.26	Argentina Chiriguanos	3.06
South Korea	1.60	Cook Islands	3.11
Ireland Northern pop2	1.64	Venezuela Bari	3.36
Senegal 1.	69	Pakistan Karachi	4.32
Spain Basque	1.70	Palestine Jordan	4.68
China Zehjiang Han	1.73	Ivory Coast Abidjan	5.40
Japan 1.	73	South Africa Xhosa	6.40
Oman 1.	84	India North Hindus	8.13
Tonga 1.	91	Venezuela Yucpa	9.87

a) KIR DS gene frequencies (Fig. **1**): The anthropologically well defined chosen populations tend to cluster in the NJ tree according to geography, unlike KIR DL-based NJ tree (Fig. **2**). In the first group, we find Asian and African populations together with Pacific populations (Samoa and Tokelau). This clustering is also confirmed in the correspondence analysis (Fig. **3**). In the middle group we have European and Mediterranean populations together with Guadaloupe (a French colony) and Oman (a mostly Mediterranean population). Thailand is also included in this group. In addition, Indian and Pacific populations show another clustering group close to this central group. Finland is placed within Europeans. This is also confirmed by the correspondence analysis (Fig. **3**). Finally, the Amerindian group is the most homogenous cluster. Mexican Mestizos show an intermediate position between Europeans / Mediterraneans and Amerindians. This is also confirmed by the correspondence analysis (Fig. **3**).

b) KIR DL allele frequencies: Both NJ (Fig. **2**) and correspondence analysis (Fig. **4**) do not show a general geographic clustering. It is remarkable that even Amerindians do not cluster together: Tarahumaras, Purepechas and Huicholes are together with Asians in the upper NJ group (Fig. **2**). Yucpa Amerindians cluster with African Xhosa and Asian Indians (Fig. **2**), which is supported by the correspondence analysis (Fig. **4**). Tokelau is placed with Amerindian groups (Fig. **2**).

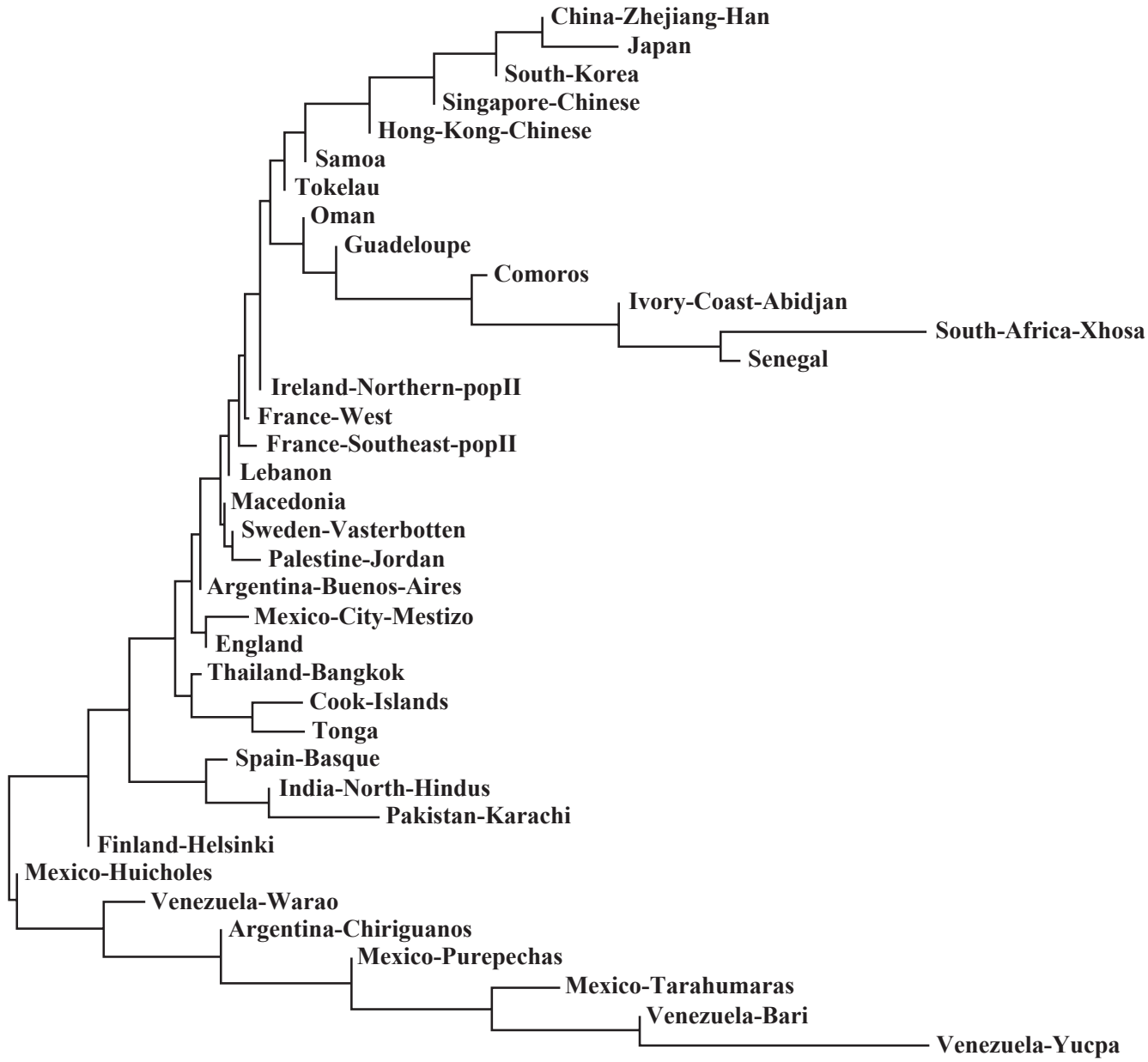

Fig. (1). Neighbour-Joining (NJ) dendrogram based on KIR DS genes. A strong trend to group populations by geographical gradient is observed (like when using HLA frequencies).

KIR haplotype B results are very similar to those of the KIR activating genes (Figs. **5**, **6**) whereas KIR haplotype A results (not shown) do not show any geographic correlation.

DISCUSSION

Our results indicate that KIR DS gene frequencies have a specific population structure and help to define the individuality of populations as HLA allele frequencies do. One may speculate whether HLA allele frequencies (HLA proteins) may shape the KIR DS frequencies repertoire, while KIR DL frequencies are shaped by a varied amount of pathogens through each population history. These findings support the idea that KIR DS genes are subjected to a kind of balancing selection (selection for variability) due to specific population pathogens. It is worthwhile mentioning that KIR DL genes/alleles from the same locus are under balancing selection in Africa [7]; this would confer KIR DS genes a strong population structure, which may or may not be related to HLA evolution. Otherwise, if HLA is shaping KIR DS gene frequencies, then the evolution forces acting on HLA genes are also acting indirectly on KIR DS. However, there is evidence that some diseases susceptibility is driven independently either by HLA or KIR inheritance [20]. This is in favour that whatever selection forces that could be acting on KIR DS genes are independent of the ones acting upon HLA genes.

On the other hand, the chance for each non-related individual to have the same KIR genes (and alleles) is really very small [10,20]; this is a feature shared with HLA system.

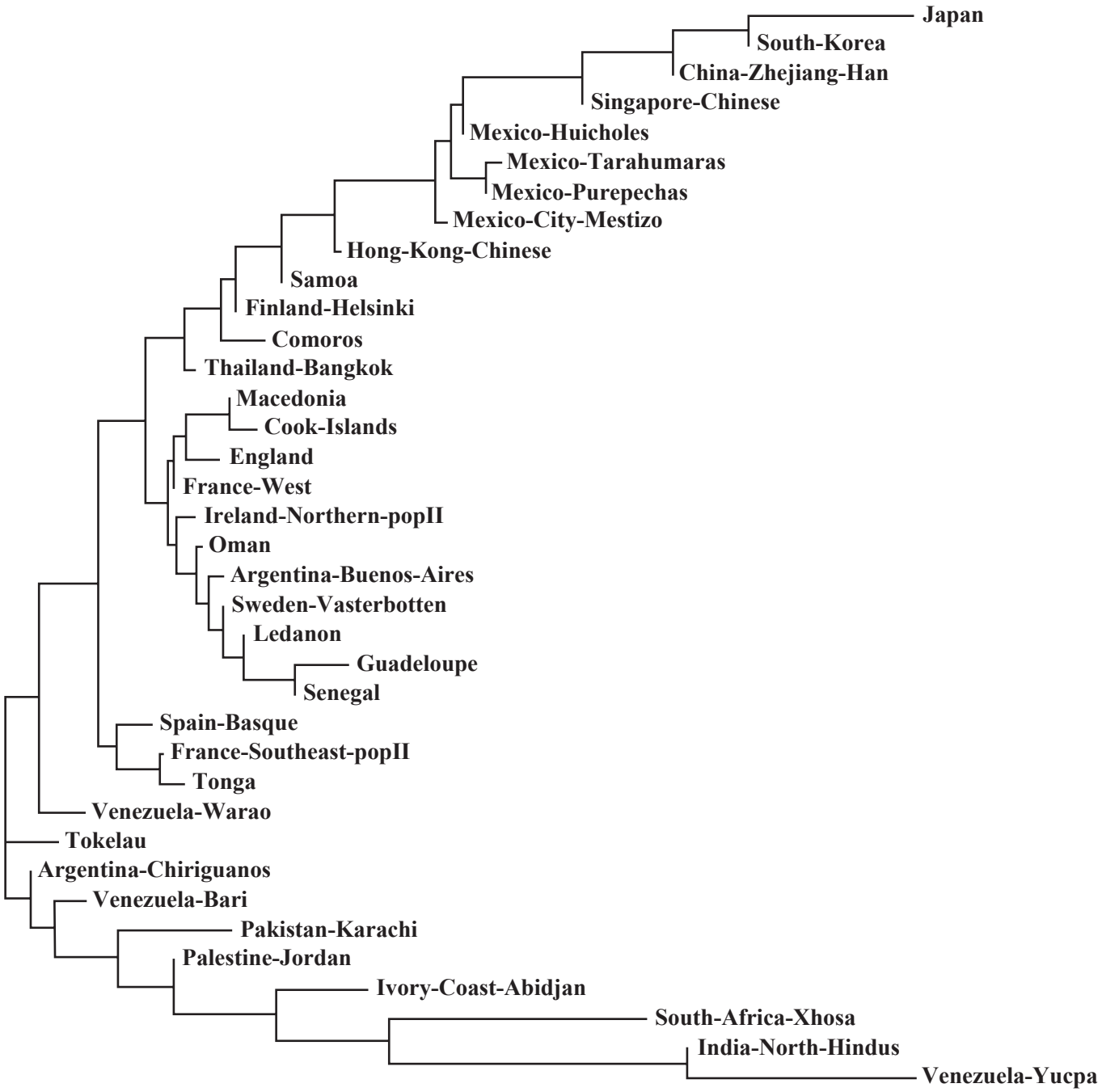

Fig. (2). Neighbour-Joining (NJ) dendrogram based on KIR DL genes.

KIR haplotype B genes also define populations by geography / anthropology parameters, similar to KIR DS genes; this is to be expected because of the genes we selected to be in each haplotype and because KIR haplotype B frequencies vary among populations much more than KIR haplotype A frequencies [20], which are very frequent in most or all tested populations. This suggests that the evolution forces that maintain KIR haplotype B frequencies among populations are similar to those that maintain KIR DS genes frequencies among populations. One may speculate that these evolution forces might include the same kind of HLA processed pathogens. We did not perform analysis of individual genes due to the fact that individual gene frequencies did not vary extensively among populations.

There is one striking exception of a population being relating by geography when KIR DS genes are analysed: Thailand-Bangkok is misplaced (Figs. **1**, **3**). No evident differences in methodology with other populations seem to have occurred. However, the results of the KIR typing have

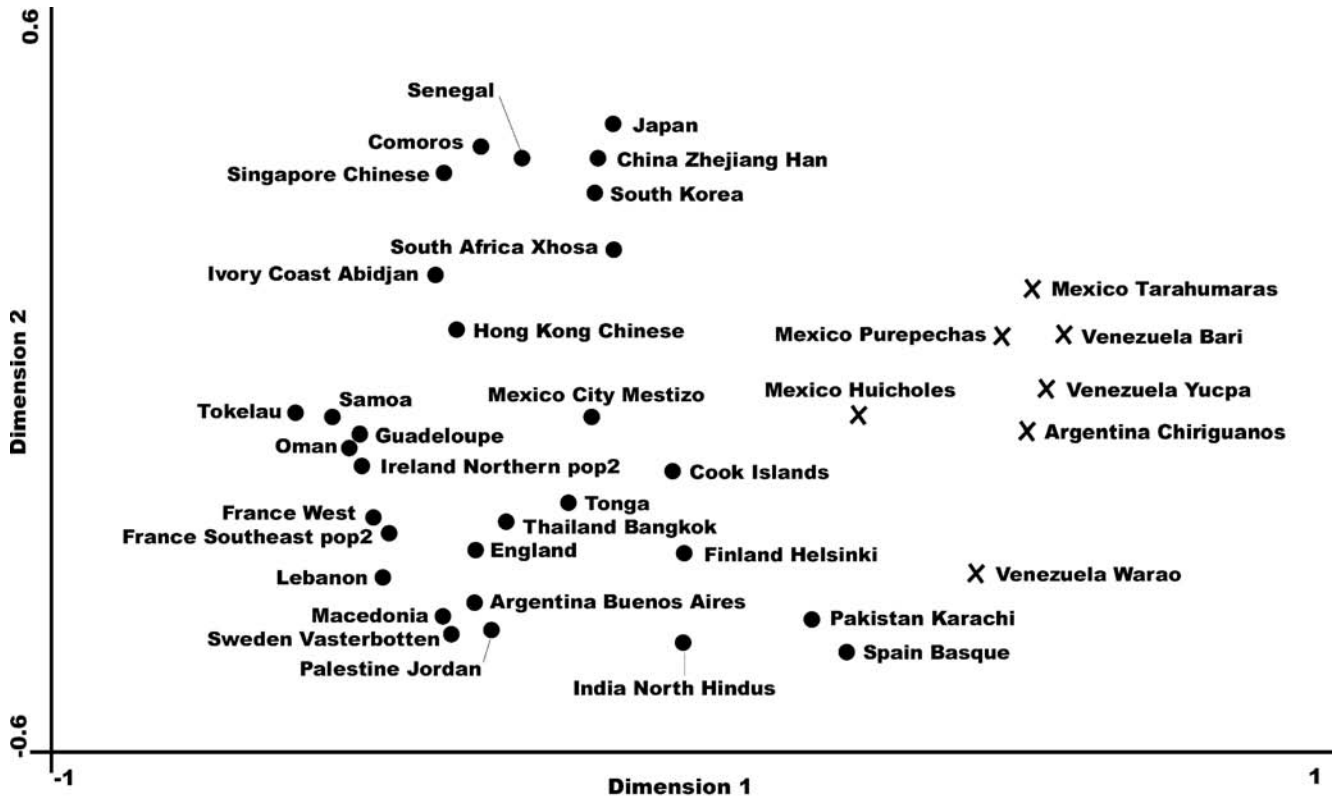

Fig. (3). Correspondence analysis based on KIR DS genes. A strong trend to group populations by geographical gradient is observed (like when using HLA frequencies). Dots represent non Amerindian populations. Crosses represent Amerindian populations.

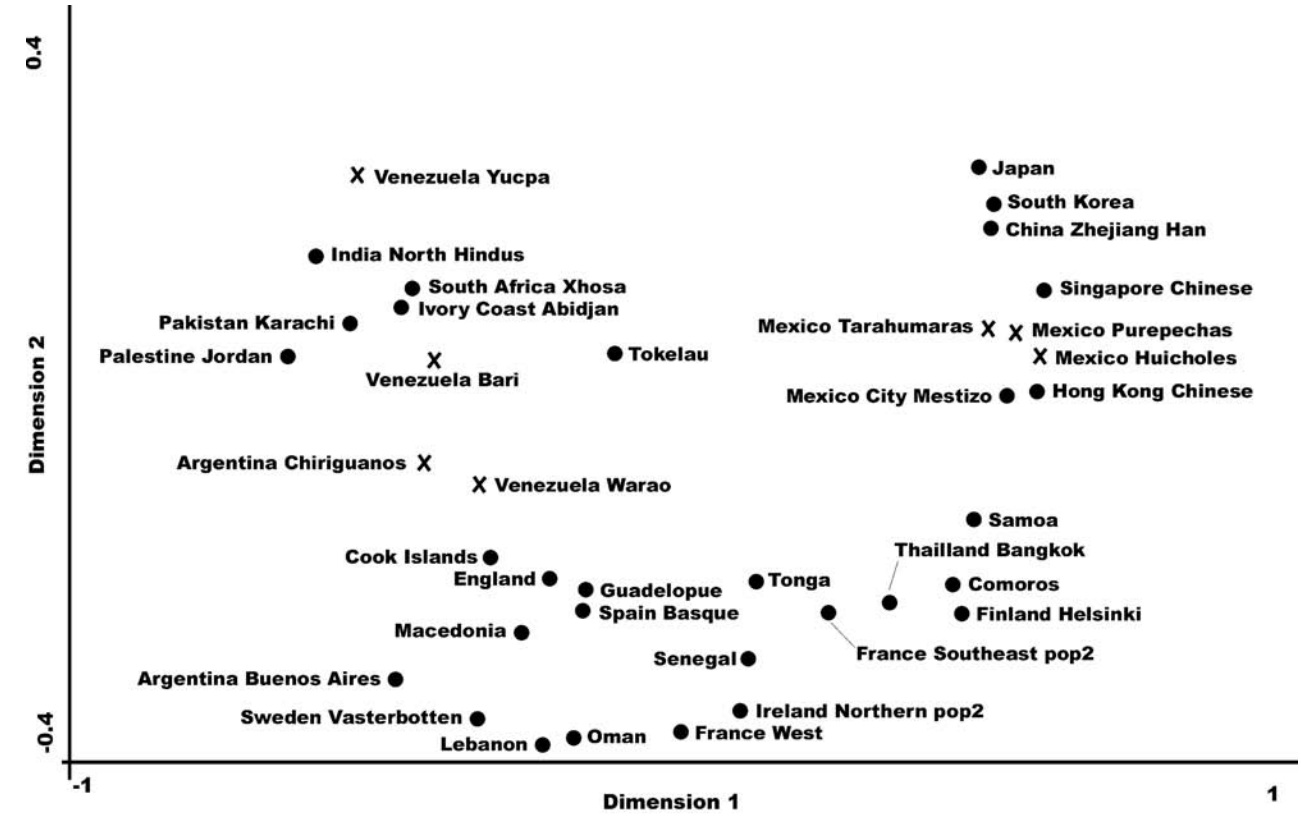

Fig. (4). Correspondence analysis based on KIR DL genes. Dots represent non Amerindian populations. Crosses represent Amerindian populations.

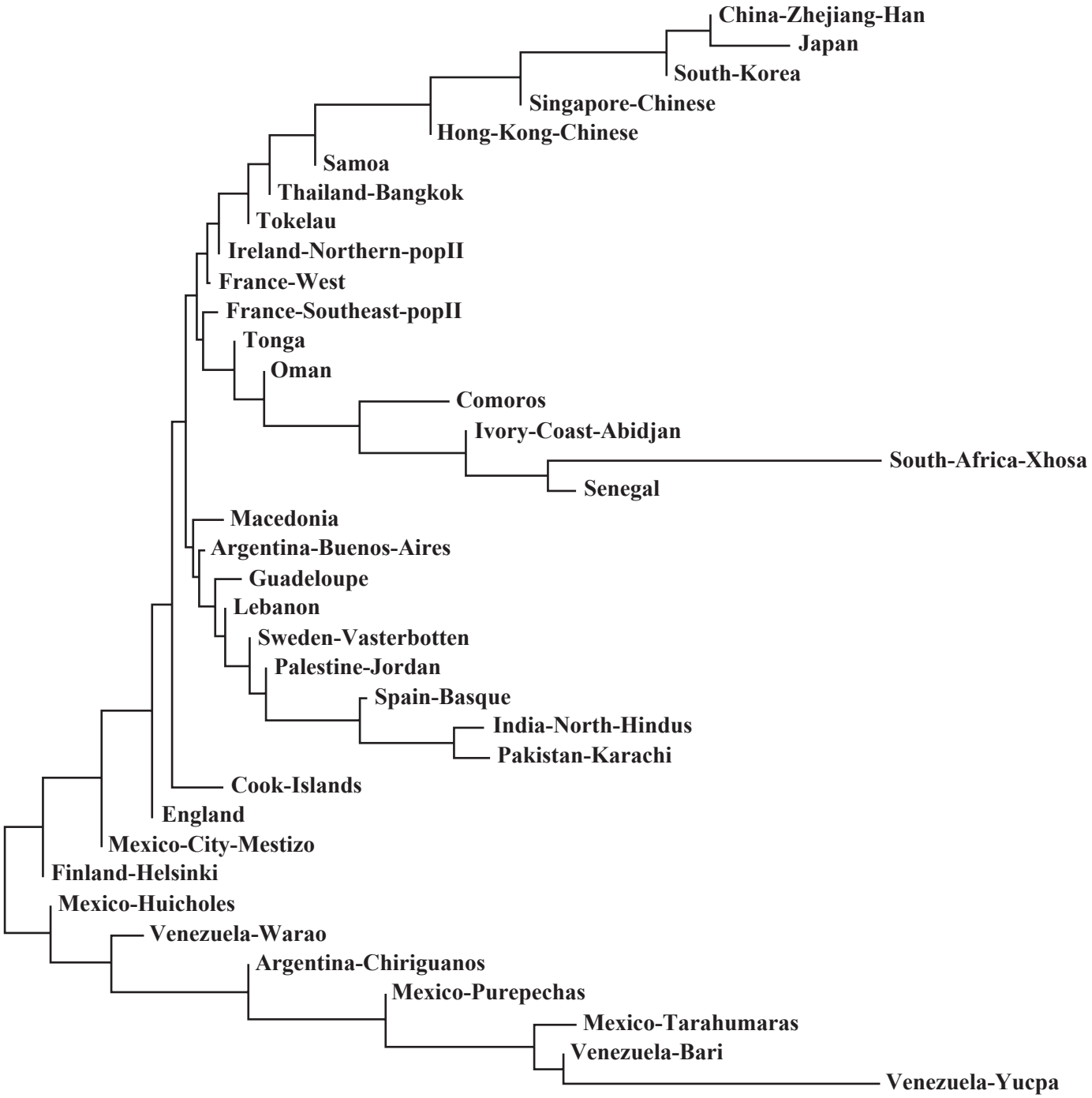

Fig. (5). Neighbour-Joining (NJ) dendrogram based on KIR haplotype B genes. A trend to group populations by geographical gradient is observed (like when using HLA frequencies).

been produced in many laboratories. There is also the possibility of sampling errors in selecting the individuals within a population. The fact that the results for the stimulatory KIR and B haplotypes correlate well with worldwide population relationships support the validity of using data from the www.allelefrequencies.net (August 25th, 2008) website for these particular (and other) analyses.

More population studies on NK KIR proteins with *a priori* well defined ethnic groups are necessary to further expand our results, which should be considered preliminary. Future studies will also need to include information on the HLA ligands in each population, information not available at present, along the lines recently taken by Single and colleagues [21] and as envisaged in a project of the 15th International Histocompatibility Workshop. In addition, knowledge will be needed as to whether the genes are functional and being used.

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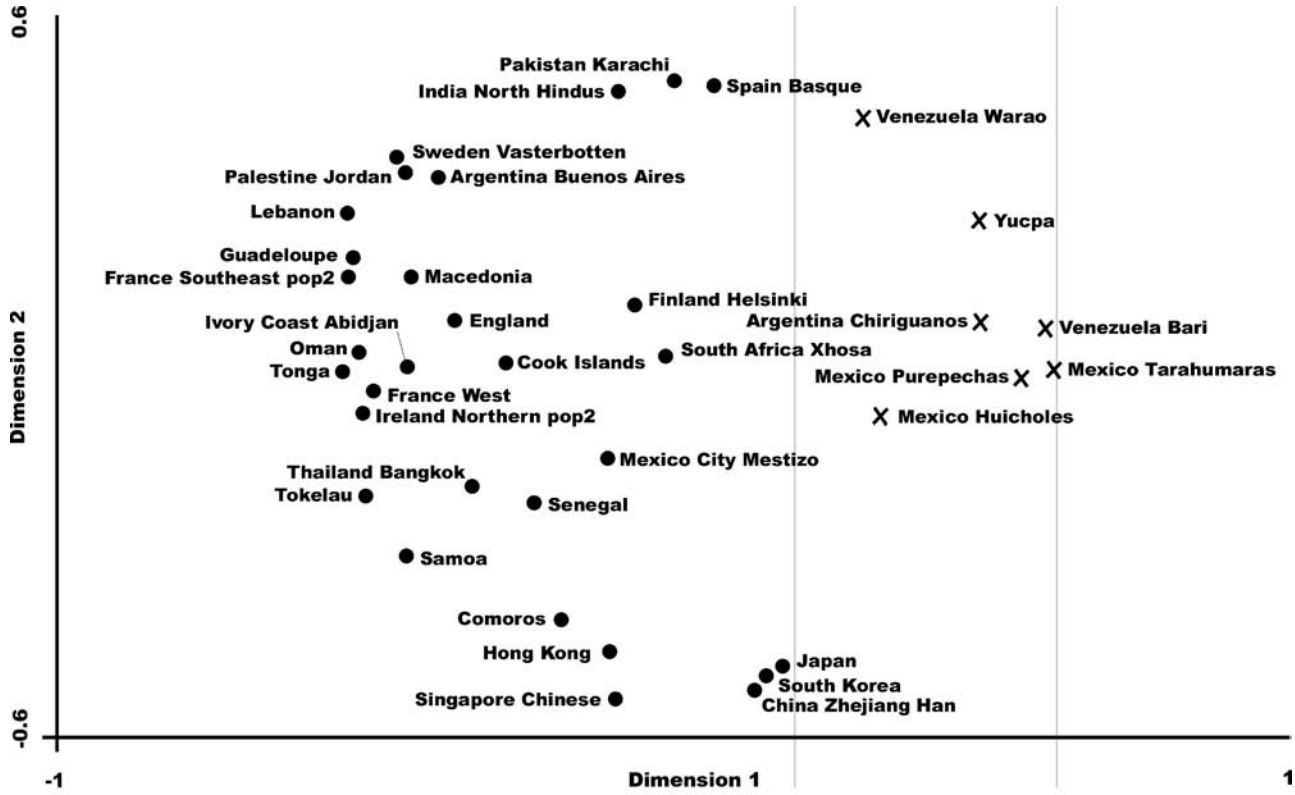

Fig. (6). Correspondence analysis based on KIR haplotype B genes. A trend to group populations by geographical gradient is observed (like when using HLA frequencies). Dots represent non Amerindian populations. Crosses represent Amerindian populations.

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