FIGURE 1 Canaan in ancient times. Palestinians (Philistines) city-states by 1100-1000 BC (black squares) Jericho was an ancient Canaanite city-state. Jerusalem, Nazareth and modern Tel-Aviv are also indicated [37]. Palestinian city-states may come from the remains of Egyptian garrisons, left to their own fate according to archaeological records [6]; the Bible quotes that Palestinians may have come from Crete [7]. Gath may be placed more to the south because it has not been recognized in modern times. Goliath, the Palestine, who was killed by King David according to the Bible, come from this city.

(1125 BC) but found the struggle with the Philistines (Palestinians) more difficult. Philistines had established an independent state on the southern coast of Palestine and also controlled the Canaanite town of Jerusalem.

The "sea people" contributed to the fall of the Anatolian Hittites and other Middle East people by 1200 BC and apparently seriously threatened Egypt [5]. The Philistines have been included among the "sea people" invaders. However, it is doubtful that big amounts of people entered nowadays Anatolia and Palestine; a new iron technology probably was taken *de novo* by some autochthonous Canaanite tribes that acquired superiority.

FIGURE 2 United Nations agreement for Palestine partition in 1947.

In fact, the Palestinians are nowadays thought to come from the Egyptian garrisons that were abandoned to their own fate on the Canaan land by 1200 years BC (Figure 1) and had to manage to construct or reinforce or rebuilt some ancient Canaanite city-states, together with the old autochthonous tribes [6]. Otherwise, the ancient Palestinians might have come from Crete or its empire [7]. Israelites could also stem from autochthonous Canaanite tribes that were agglutinated by a group of people led by Moses to fight against other Canaanites, including Philistines and finally set up ancient Israel [6-8]. By 1000 BC, and after warring with Philistines and other Canaanites, an Israelite state was founded by king Saul [6].

Palestinians held five important city-states when the fighting with Israel began (after 1200 BC): Gaza, Ash-

FIGURE 3 Location of the studied populations and map of the present day Israel-Palestine. The Palestinian Autonomous Government has a limited rule in the Gaza Strip and West (Jordan) Bank.

kelon, Ashod, Ekron and Gath (Figure 1). They won several battles and the time that they were in control of all Canaan, west to the Jordan river (about 100 years?) has been enough to name the land as Palestine until after World War II [9]. They probably had an iron technology higher than Israelites, because they did not let Israelites to work as blacksmiths when they were ruling over Israelites [see *Bible* starting in Samuel 13 and 19; 5,7].

Alexander the Great [9] surrendered Gaza after a long siege about 333 BC. Later, Gaza became an important Christian center [9] and afterwards an important Islamic center because Palestine was converted to Islam by Arabic troops and priests by 700 AD [9]. Ancient Canaan (Palestine in Middle Age and modern times) has sequentially belonged to the Roman-Byzantine empire, to Egyptian Muslim Mammeluks, to the European crusaders and finally to the Ottoman-Empire [9] since the XVI century. In 1918 British led mixed Arab-British troops seized the region. Palestine had 750,000 inhabitants in 1919 [9] and only 70,000 were Jewish. Immigration rapidly increased the number of Jews (who had been several times led to Diaspora, expelled, deported, and massacred by ancient Iranians and Romans, most western European countries, and finally Hitler [8,9]). There were 400,000 Jews present in Palestine by 1936 and 600,000 by 1947 when Palestine population amounted 2,000,000 inhabitants. The United Nations plan for Palestine partition in 1947 is illustrated in Figure 2 [9]. Israel´s self-proclaimed independent in 1948 and started a war against Muslim Palestinians and other Muslim neighbouring countries. After several regional wars, Israel has taken more space and sized Jerusalem, as illustrated in Figure 3. The present situation (April 2001) is unstable.

Palestinians were about 5,000,000 at the beginning of the last decade. Nowadays, they might reach 7,000,000 [9-11]. Three kind of Palestinians, according to their status, may be defined as follows: (1) the inhabitants under an autonomous Palestinian government (about 30%) that controls very little of the West Jordan Bank

TABLE 1 Populations used for the present study

Identification number	Population	Number [a]	Reference	Identification number	Population	Number [a]	Reference
1	Palestinians	165	Present study	18	Egyptians (Siwa)	101	3
2	Berbers (Souss)	98	37	19	Armenians	105	16
3	Moroccan Jews	94	38	20	Turks	228	21
4	Ashkenazi Jews	80	8	21	Iranians	100	39
5	Non-Ashkenazi Jews	80	8	22	Senegalese	192	16
6	Lebanese KZ [b]	93	3	23	Bushmen (San)	77	16
7	Lebanese NS [c]	59	3	24	South African Blacks	86	16
8	Italians	284	16	25	South American Blacks	59	16
9	French	179	16	26	Greeks (Aegean)	85	3
10	Spaniards	176	27	27	Greeks (Attica)	96	3
11	Portuguese	228	18	28	Greeks (Cyprus)	101	3
12	Spanish-Basques	80	27	29	Oromo	83	3
13	Sardinians	91	16	30	Amhara	98	3
14	Cretans	135	19	31	Fulani	38	3
15	Macedonians	172	20	32	Rimaibe	39	3
16	Algerians	102	17	33	Mossi	42	3
17	Moroccans	98	28	34	Japanese	493	16

[a] Number of individuals analysed for each population; [b] KZ= Kafar Zubian (town); [c] NS= Niha el Shouff (town). (See Ref. [41].)

(inhabited by more than 1,500,000 Palestinians), but controls more in the Gaza strip (about 1,000,000 Palestinians), where Palestinians have to lived mixed with Jewish colonist in their theoretically own territories; (2) the Diaspora Palestinians (occurred after 1947), who have refugee status (about 40%, [9,10]), and live either in concentration camps or are scattered in Jordan (38%), Syria (12%) and Lebanon (13%). Saudi Arabia and Kuwait gather about 500,000 Palestinians; Egypt, Iraq and other Mediterranean, European and American countries have more reduced communities; and (3) the Israel Palestinians, who live within Israel (37%). Most of Palestinians profess Muslim religion, but there are also Druze and Christian minorities [10]. They speak the Palestinian-Arab dialect [10].

The aim of the present study is to examine the genetic relationships of Palestinians with their neighbours (particularly the Jews) and other Mediterranean populations in order to: (1) discover the Palestinian origins, and (2) explain the historic basis of the present day Middle East conflict between Palestinians and other Muslim countries with Israelite Jews.

MATERIAL AND METHODS

Population samples

Samples from 165 unrelated Palestinians in Gaza (Laboratories and Blood Bank, El-Shifa Hospital, Gaza) were used for HLA genotyping and phylogenetic calculations. All were selected in order that their ancestors (eight grandparents) had a Palestinian origin. This sample may be considered as representative of the Palestinian population because many people have been forced to live in the Gaza strip, coming from other parts of Palestine, and the Gaza strip is now a relatively or totally (when the ongoing conflict aggravates) secluded area. All other populations used for comparisons are detailed in Table 1 and Figure 3.

HLA Genotyping, DNA Sequencing and Statistics

Generic HLA class I (A and B) and high resolution HLA class II (DRB1 and DQB1) genotyping was performed using a reverse dot-blot technique with the Automated Innolipa system (Innogenetics N.V., Zwijndrecht, Belgium). HLA-A, -B, -DRB1, and -DQB1 allele DNA sequencing was only done when indirect DNA typing (reverse dot-blot) yielded ambiguous results [12]. Statistical analysis was performed with Arlequin v1.1 software kindly provided by Excoffier and Slatkin [13]. In summary, this program calculated HLA-A, -B, -DRB1 and -DQB1 allele frequencies, Hardy-Weinberg equilibrium and the linkage disequilibrium between two alleles at two different loci. Linkage disequilibrium (D´; also named LD, see Imanishi et al. [14]) and its level of significance (p) for 2 x 2 comparisons were determined using the formulae of Mattiuz and co-workers [15] and the 11th International Histocompatibility Workshop methodology [14].

In addition, the most frequent complete haplotypes were deduced following a methodology used in the 11th International Histocompatibility Workshop: (1) the 2, 3, and 4 HLA loci haplotype frequencies [3,16-21]; (2) the

haplotypes previously described in other populations [3,16]; and (3) haplotypes that were assigned if they appeared in two or more individuals and the alternative haplotype was well defined. In order to compare allelic and haplotype HLA frequencies with other populations, the reference tables used were those of the 11th and 12th International HLA Workshops [3,16]; see also Table 1. Phylogenetic trees (dendrograms) were constructed with the allelic frequencies by applying the Neighbor-Joining (NJ) method [22] with the genetic distances between populations (DA, [23]) and using DISPAN software containing the programs GNKDST and TREEVIEW [24,25]. A three-dimensional correspondence analysis and its bidimensional representation was carried out using the VISTA v5.02 computer program ([26]; http:/ forrest.psych.unc.edu). Correspondence analysis comprises a geometric technique that may be used for displaying a global view of the relationships among populations according to HLA (or other) allele frequencies. This methodology is based on the allelic frequency variance among populations (similar to the classical principal components methodology) and on the display of a statistical projection of the differences.

RESULTS

Characteristic HLA Allele Frequencies of the Palestinian Population Compared With Other Mediterraneans

The expected and observed gene allelic frequencies for HLA-A, -B, -DRB1 and -DQB1 loci do not significantly differ and the population sample is in Hardy-Weinberg equilibrium. Table 2 illustrates the HLA allele frequencies found in the Palestinian population. Seventeen HLA-A and 26 different HLA-B alleles were observed in the Palestinian population. Seven HLA-A and seven HLA-B alleles had frequencies higher than 5% (A*01, A*02, A*03, A*23, A*24, A*30, A*32, B*18, B*35, B*41, B*44 B*49, B*50, and B*51) and these are characteristic of Mediterranean populations, particularly from eastern Mediterranean regions [17,19-21,27,28]. With regard to the HLA class II alleles, 31 different DRB1 alleles were found and only seven had frequencies higher than 5% (DRB1*0301, *0403, *0406, *0701, *1101, *1104, *1303) being also characteristic of eastern Mediterranean populations. In particular, DRB1*0403 is present in high frequency in Lebanese [29], North African and Jewish populations [8,17]; DRB1*0406 is also present in North Africans populations [17,28]. Besides, DRB1*0302 (allele frequency 3.3%), characteristic of African Black populations, is also present in North African Caucasians, Jews and Lebanese [8,17,28,29]. DQ allele frequencies reflect the DRB1 locus allele distribution due to the strong linkage disequilibrium between these two loci.

Three types of analyses were carried out to compare Palestinian HLA frequencies with other Mediterranean population frequencies: (1) with DRB1-DQB1 data, which is probably a more informative and discriminating methodology; (2) with DRB1 data; and (3) with generic (low resolution) DR-DQ data. These three types of analysis were performed because some of the populations used for comparison lacked HLA-A and -B data (Berbers [from Souss, Agadir area], Jews [Ashkenazi], Jews [Morocco], Jews [non-Ashkenazi], Lebanese [NS and KZ], see Table 1), or high resolution HLA-DQ data (Greeks [Attica], Greeks [Cyprus], Greeks [Attica-Aegean], see Table 1), or only generic HLA-DR and –DQ data were available (Portuguese, Turks, Iranians, Armenians and Egyptians, see Table 1). These partially HLA-typed populations should have been ignored, but they could be analyzed conjointly taking into account only either DRB1 or generic DR and DQ frequencies (Table 3, Figsures 1, 2, 3, 4 and 5).

Analyses using DRB1 and DQB1 conjointly were made but are not illustrated because only a few populations could be used and the results are concordant with the DRB1 analysis. Finally, it should be pointed out that class I generic typing tends to homogenize the comparisons based on DRB1 high resolution typing [28]; one class I allele obtained by generic DNA typing may contain several class I alleles, whereas this is not the case for most DRB1 alleles at present.

Figure 4 depicts an HLA class II "high-resolution" (DRB1) NJ tree. Populations are grouped into three main branches: the first one groups both eastern (including Palestinians, Macedonians, Cretans, Jews, Lebanese) and western Mediterranean populations (Europeans and North Africans; Sardinians are included in the first group). The second branch is formed by African Negroid populations and Japanese (Mediterranean outgroups) and the third one includes Greek and Ethiopian/sub-Saharan populations. This distribution is also confirmed in the correspondence analysis (Figure 5): the three groups are clearly delimited and an smooth West to East Mediterranean gradient is shown. The Palestinian population reveals the closest genetic distance with Jews (generic DR-DQ typing), Cretans (using DRB1-DQB1) or Algerians (using DRB1) (see Table 3) and no discontinuity is observed between eastern and western Mediterranean populations reflecting the genetic similarity among all these populations. It is evidenced that Palestinians/Greeks distance is high and confirms the different genetic background of the Greeks, who have received a substantial sub-Saharan gene flow [3,20].

These results are confirmed using DR and DQ generic typings (see Table 3 and Figure 6) which were used in

TABLE 2 HLA-A, -B, -DRB1, and -DQB1 allele frequencies in the Palestinian population.

Alleles	Allele frequencies %	Alleles	Allele frequencies %	Alleles	Allele frequencies %
HLA-A		B*53	2.4	HLA-DQB1*	
A*01	12.4	B*55	1.5	02	20.9
A*02	20.3	B*56	0.3	0301	26.7
A*03	10.6	B*57	1.8	0302	17.6
A*11	3.9	B*58	2.4	0303	2.4
A*23	7.5			0402	4.8
A*24	10.0	**HLA-DRB1***		0501	11.8
A*26	3.3	0101	0.9	0502	0.6
A*29	2.4	0102	4.5	0503	3.9
A*30	8.4	0301	7.6	0601	1.8
A*31	1.2	0302	3.3	0602	4.2
A*32	6.0	0309	0.3	0603	1.2
A*33	3.6	0401	1.2	0604	3.9
A*66	0.9	0402	3.3		
A*68	3.6	0403	9.3		
A*69	4.8	0404	3.3		
A*74	0.3	0405	1.5		
A*80	0.3	0406	6.1		
HLA-B		0408	0.3		
B*07	1.8	0701	12.7		
B*08	2.7	0804	0.3		
B*13	2.4	0901	1.2		
B*14(B65)	4.2	1001	3.9		
B*15(B62)	2.4	1101	10.0		
B*18	5.8	1102	0.3		
B*27	1.5	1103	0.3		
B*35	20.3	1104	9.7		
B*37	0.6	1201	0.9		
B*38	1.8	1301	0.9		
B*39	1.2	1302	3.9		
B*40(B60)	3.3	1303	5.5		
B*41	7.6	1305	1.2		
B*42	2.4	1334	0.3		
B*44	9.6	1401	3.9		
B*45	1.5	1501	3.6		
B*47	1.5	1502	2.1		
B*49	6.9	1503	2.1		
B*50	5.8	1601	0.6		
B*51	6.4				
B*52	1.5				

Alleles DQB1*0201 and 0202 were all assigned as DQB1*02. Number in brackets indicates the serologic antigen most probably corresponding to the genetic allele obtained.

order to include other Mediterranean populations (Iranians, Armenians, Egyptians and Turks, see Table 1). The close relatedness of Palestinians (Table 3 first column, Figure 6) to Iranians, Armenians, Egyptians and Anatolians (Turks [21]) further support an autochthonous Canaanite/Middle East origin for both Palestinians and Jews. A DR-DQ neighbour-joining tree (not shown) maintains the west and east Mediterranean groups and also the group formed by Greeks and sub-Saharan populations. Turks (old Anatolians), Armenians, Jews and Lebanese are illustrated specifically to cluster with Palestinians. On the other hand, genetic distances obtained by using DR-DQ generic typing allele frequencies (Table 3) illustate that Ashkenazi Jews, Iranians, Cretans, Armenians, Turks and non-Ashkenazi Jews are the populations closest to the Palestinians, followed by the other Mediterraneans populations. Other analyses and genetic distances confirm these results (Table 3, Figures 4 and 5).

HLA-A, -B, -DRB1, and -DQB1 Linkage Disequilibria in Palestinians

Extended HLA haplotypes were defined in Palestinians and compared with those previously reported in other populations (Table 4).

HLA-A-B and DRB1*-DQB1* two-loci linkage disequilibrium data (not shown) show that the most

TABLE 3 Genetic distances (DA) between the Palestinians and other populations (x 10^2) obtained by using generic HLA-DR-DQ, and high-resolution HLA-DRB1 and HLA-DRB1-DQB1 allele frequencies (see Table 1 for identification of populations).

HLA-DR-DQ (DA)		HLA-DRB1 (DA)		HLA-DRB1-DQB1 (DA)	
Ashkenazi Jews	1.61	Algerians	12.33	Cretans	9.50
Iranians	2.25	Cretans	12.47	Moroccans	9.53
Cretans	2.28	Non-Ashkenazi Jews	12.48	Spaniards	11.33
Armenians	3.08	Moroccans	13.15	Non-Ashkenazi Jews	11.53
Turks	3.12	Lebanese-KZ	13.82	Lebanese-KZ	12.32
Non-Ashkenazi Jews	3.17	Spaniards	14.39	Algerians	12.70
Spaniards	3.25	Moroccan Jews	15.37	Moroccan Jews	12.81
Portuguese	3.37	Italians	15.60	Ashkenazi Jews	13.32
Algerians	3.45	Lebanese-NS	16.92	French	14.09
Lebanese-KZ	3.63	Ashkenazi Jews	17.28	Italians	14.24
Macedonians	4.04	French	17.82	Macedonians	15.50
French	4.34	Macedonians	20.39	Lebanese-NS	15.62
Moroccans	4.51	Berbers (Souss)	20.72	Berbers (Souss)	15.99
Moroccan Jews	4.61	Sardinians	23.62	Sardinians	19.78
Egyptians	5.64	South African Blacks	27.83	Spanish-Basques	25.27
Sardinians	5.67	Spanish-Basques	33.27	South African Blacks	32.83
Italians	6.52	Greeks (Attica)	34.36	Japanese	34.41
Berbers (Souss)	6.65	Oromo	38.56	Senegalese	36.48
South American Blacks	7.71	Senegalese	39.56	San (Bushmen)	40.92
South African Blacks	8.00	Amhara	42.95		
Senegalese	9.27	Greeks (Cyprus)	43.67		
Spanish-Basques	9.95	Japanese	46.36		
San (Bushmen)	10.55	Greeks (Aegean)	48.73		
Oromo	11.38	San (Bushmen)	53.25		
Amhara	11.93	Mossi	57.36		
Greeks (Attica)	14.54	Fulani	58.33		
Japanese	17.96	Rimaibe	64.37		
Mossi	24.66				
Fulani	25.01				
Rimaibe	30.85				

frequent combinations are characteristic of Mediterranean (western and eastern) populations (A*1-B*35, haplotype Frequency (HF): 5.1; B*35-DRB1*1104, HF: 3.2; B*35-DRB1*0403, HF: 3.2; A*2-B*41, HF: 3.1; A*2-B*51, HF: 2.9; B*18-DRB1*1104, HF: 2.8; B*49-DRB1*0403, HF: 2.7; A*24-B*35, HF: 2.3; A*23-B*44, HF: 2.3; A*24-B*18, HF: 2.1; B*14-DRB1*0102, HF: 2.0; B*35-DRB1*1101, HF: 2.0; A*33-B*14, HF: 1.7; B*49-DRB1*1001, HF: 1.6; B*35-DRB1*1001, HF: 1.5; B*50-DRB1*0701, HF:1.5; B*8-DRB1*0301, HF: 1.5). The combination A*69-B*49 (HF: 2.7) has not been found in any of the populations tested and it is included in an extended haplotype (A*69-B*49-DRB1*0403-DQB1*0302, see below) not previously described.

The HLA-A-B-DR-DQ extended haplotypes found in the Palestinian population (Table 4) reflect common characteristics with the other "older" Mediterranean population mainly from eastern Mediterraneans and North Africans (see footnote to Table 4), like Jews [8]. These haplotype results are concordant with those obtained by the allele frequency analyses (genetic distances, NJ trees and correspondence analyses, see above).

DISCUSSION

Palestinians and Jews

The genetic identity of Ashkenazi and non-Ashkenazi Jews who now lives in Israel has already been reported [8]. Babylonian and Roman-induced Diaspora, drove Jews to many parts of Europe, Africa and Asia, which occurred in 587 BC and 70 AD, respectively. Jews started to come back to Palestine during the 19th and 20th centuries [8]. However, religion and close communities have kept Jews relatively isolated from the inhabitants of the countries that hosted them during this long period of time. Jews wrote the Bible, a religious and historical book that is a continuous source of historical Middle East facts, but that only tells the Jewish view [6]. It is now necessary to rely on other sources, such as archaeology, linguistics, etc, to establish a more objective history of Middle East and particularly ancient Canaan [6,9].

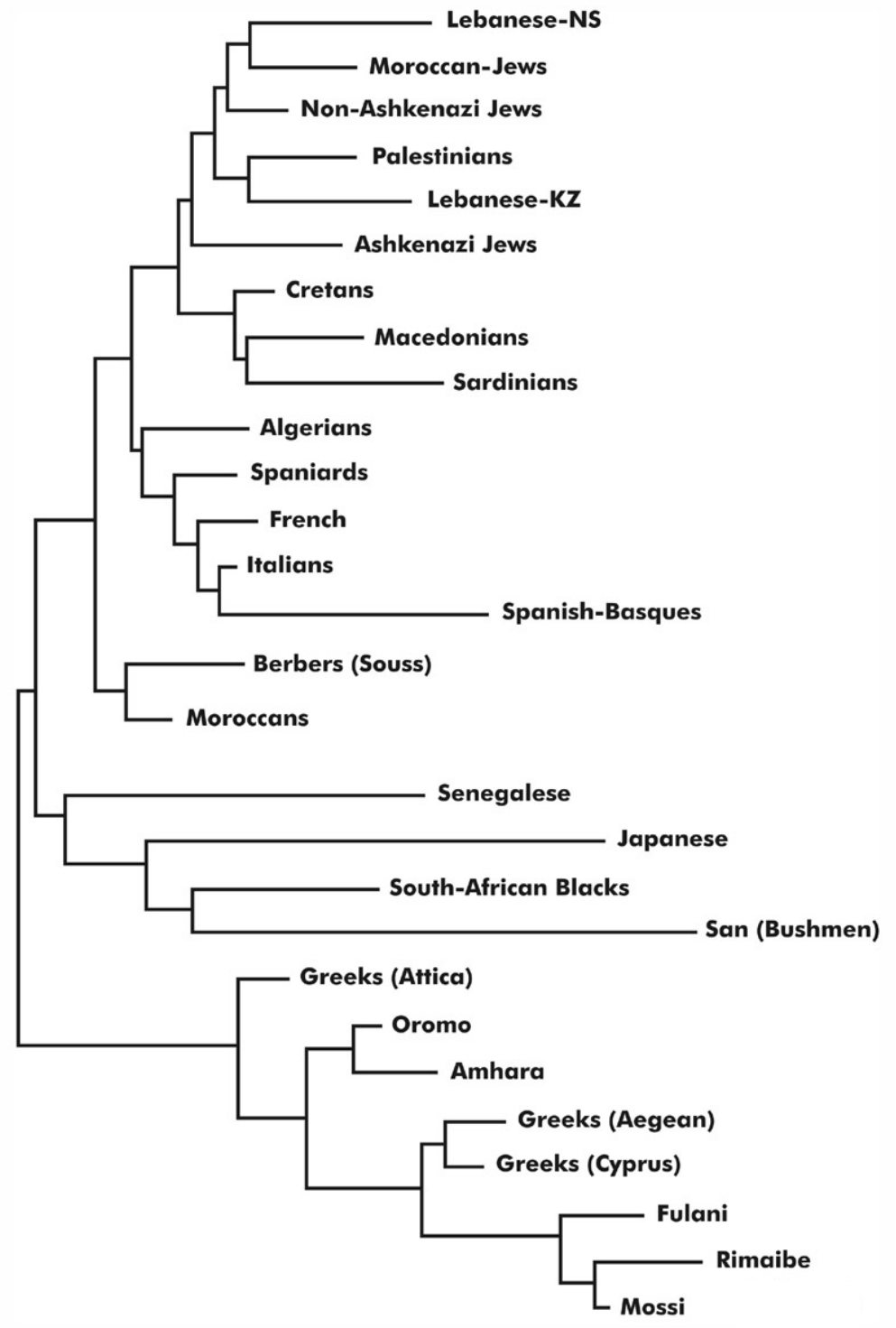

FIGURE 4 Neighbor-Joining dendrogram demonstrating relatedness between Palestinians and other populations. Genetic distances between populations (DA) were calculated by using HLA-DRB1 (high resolution). Data from other populations were from references detailed in Table 1. Bootstrap values from 1000 replicates are illustrated.

Palestinians appeared in the Bible as coming from Crete or its empire [7]. The present day concept based in archaeology is that most original Palestinians were already in Canaan and some tribes were agglutinated by Egyptian garrisons, left to their own fate in Canaan [6]; but the input of one "elite" coming from Crete may not

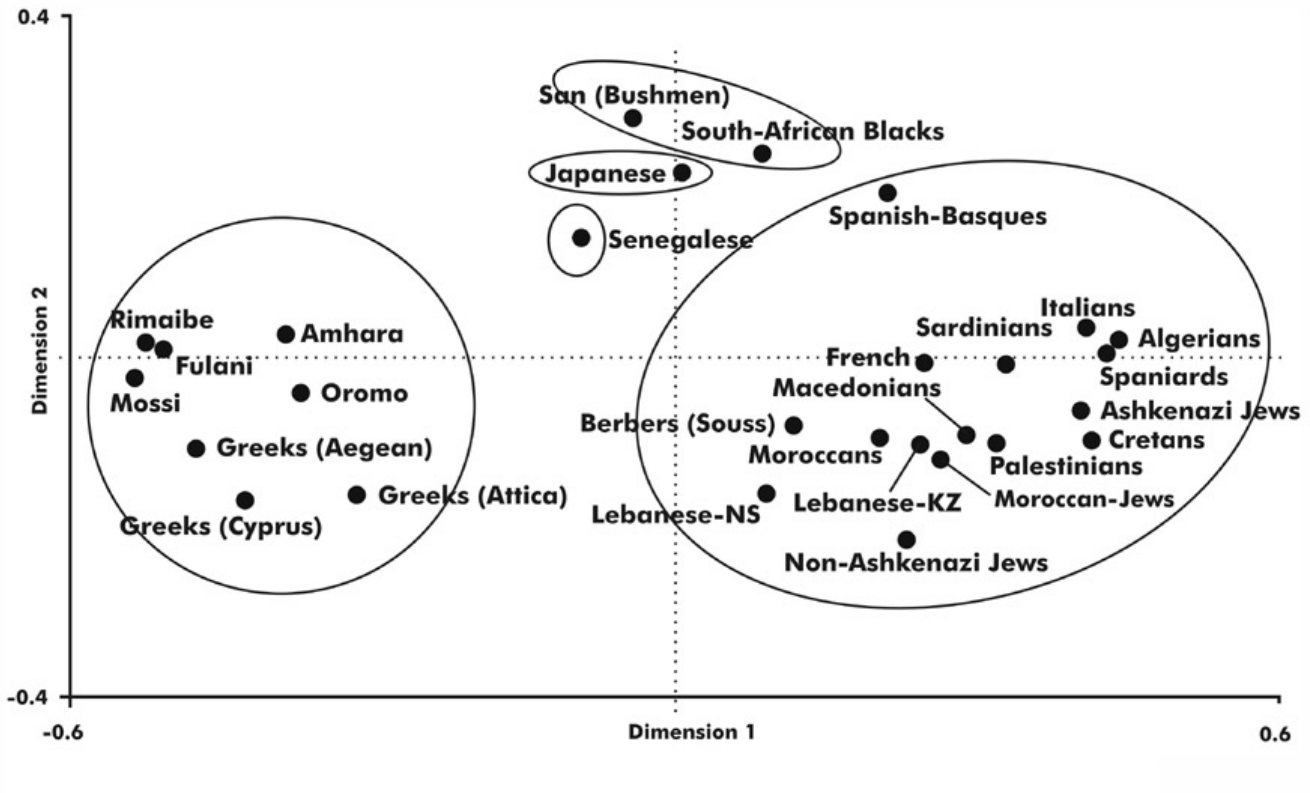

FIGURE 5 Correspondence analysis depicting a global view of the relationship between Mediterraneans and Palestinians according to HLA allele frequencies in three dimensions (bidimensional representation). HLA-DRB1 allele frequencies data.

be discarded. Also, the bulk of Jewish people probably came from ancient autochthonous Canaanites [6]; this is compatible with an input of foreign leaders and their groups (Abraham, Moses) as described in the Bible [7].

Both Jews and Palestinians share a very similar HLA genetic pool (Table 3, Figures 4, 5 and 6) that support a common ancient Canaanite origin. Therefore, the origin of the long-lasting Jewish-Palestinian hostility is the fight for land in ancient times. Religious and cultural have enhanced the conflict in the last centuries, together with the massive European, American, Asian and African Jews settlements in the area, which has also caused a massive displacement of Palestinians and wars. A difficult problem has now been created between two communities that are close genetic relatives.

Regarding Palestinian population identity, it is clear that they spoke a language different to Arab or Jewish in ancient times and only a few words have been preserved. Palestinians named their leaders or princes as "seren" (Basque, Zar = old man, en = the most important) [7]. The study of this and other words suggests that they spoke a Dene-Caucasian language like other Mediterranean populations [30,31]. The typical Philistine crest-hut already appeared in the Cretan Phaistos Disk (1600 BC) and in the Ramses III-Medinet Habu temple, Egypt (1200 BC, [5]).

The Eurocentric confusion "Arab = Muslim" has also lowered the Palestinian identity by identifying the country were Mohammed was born (Saudi Arabia) with the Muslim religion; it also has artificially divided peoples both coming from ancient Canaanites (Jews and Palestinians).

Palestinians and Other Middle East and European People

Palestinians are close to Egyptians, Lebanese, Iranians, Cretans, Macedonians and Sardinians, and also to Algerians, Spaniards, French, Italians and Basques (Table 3, Figures 4, 5, and 6). DRB1 genetic distances (Table 1) are probably the most reliable ones due to the higher polymorphism detected in this locus. The western and eastern Mediteranean populations are intermingled in this case; it supports the long-standing prehistoric and historic circum-Mediteranean gene flow [32]. Jews, Cretans, Egyptians, Iranians, Turks and Armenians are probably the closest relatives to Palestinians and this favors the hypothesis that most of the HLA Palestinian genetic background comes from the Middle East (ancient Canaan, [6]), ancient stock, *i.e.*: ancient Canaanites.

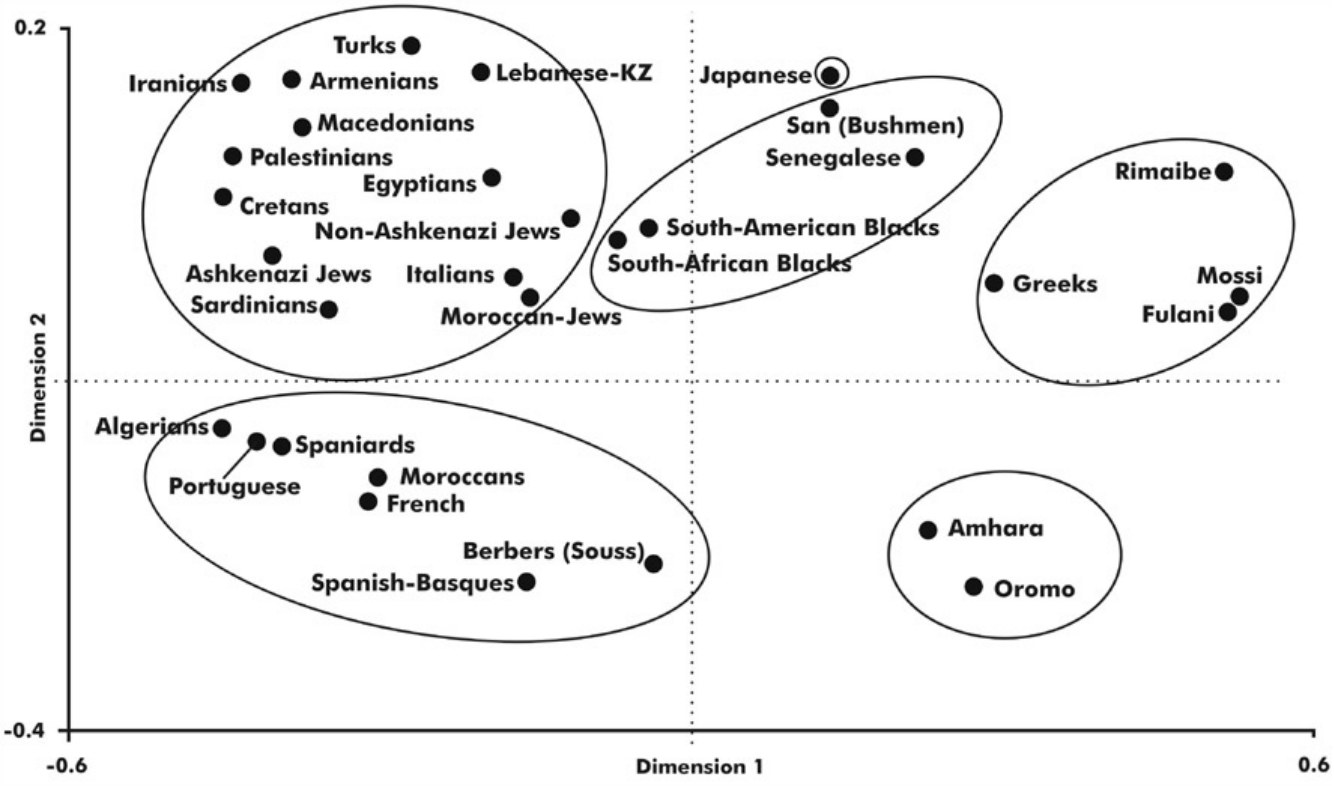

FIGURE 6 Correspondence analysis depicting a global view of the relationship among Palestinians, West Mediterraneans, East Mediterraneans, Greeks and sub-Saharian populations and Blacks according to HLA allele frequencies in three dimensions (bidimensional representation) . HLA-DR and DQ (low resolution) allele frequencies data.

Canaan had received gene and cultural flow from Mesopotamia, Anatolia and Egypt [6].

Palestinians, Cretans and Greeks

The Biblical origin for Palestinians (Crete) cannot be disregarded [7] because an "elite" group could have joined to Canaanite proto-Palestinian tribes and made themselves noticeable; this is supported by the ancient Palestinians high war technology and the many confrontations with the Jews after 1500 BC [6,7].

It is very unlikely that a massive immigration of Palestinians came from Crete [6]. Egyptian garrisons in Canaan abandoned to their fate by the Egyptian Kingdom weakness may have catalyzed the union of some Canaanite tribes to become the historical Palestinians, according to Amelie Kuhrt [6].

By 1500-1200 BC the Greek presence was very scarce in Canaan, according to archaeologic records [6]. In fact, the "Mycaenian" Greeks attacked Crete by 1450 BC after rendering tributes to Cretans by a relatively long period. The Cretan Aegean Sea empire was destroyed and continued by the Mycaenians. Greeks are found to have a substantial HLA gene flow from sub-Saharan Ethiopian and Black people [3,20]. This is why Greeks are Mediterranean outliers in all kind of analyses [19-21,28]. This African genetic and cultural input was documented by Herodotus [33] who states that the daughters of Danaus (who were black) came from Egypt in great numbers to settle in Greece. Also, ancient Greeks believed that their religion and culture came from Egypt [33]. An explanation of the Egypt-to-Greece migration may be that a densely populated Sahara (before 5000 BC) may have contained an admixture of Negroid and Caucasoid populations, and some of the Negroid populations may have migrated by chance or unknown causes towards present day Greece [19,34-36].

This could have occurred when hyperarid Saharan condition become established and large-scale migration occurred in all directions out from the desert. In this case, the most ancient Greek Pelasgian substratum would come from a Negroid stock. A more likely explanation is that at an undetermined time during Egyptian pharaonic times a Black dynasty with their followers were expelled and went towards Greece where they settled [20, 30].

Once an African input to the ancient Greek genetic pool is established, it remains to be determined what the

TABLE 4 Most frequent HLA-A, -B, -DRB1, and -DQB1 extended haplotypes in the Palestinian population and their possible origin.

Haplotypes	HF (%)	Possible origin
A*69-B*49-DRB1*0403-DQB1*0302a	2.4	Palestinian/ Mediterranean
A*01-B*35-DRB1*1104-DQB1*0301b	1.8	Mediterranean/ Central European
A*24-B*18-DRB1*1104-DQB1*0301c	1.8	Central-South-Eurasian
A*03-B*35-DRB1*0701-DQB1*02d	1.5	Mediterranean/ Central European
A*02-B*41-DRB1*0701-DQB1*02	1.5	Palestinian
A*01-B*35-DRB1*1101-DQB1*0301e	1.2	Mediterranean/ Central European
A*24-B*35-DRB1*1101-DQB1*0301f	1.2	Mediterranean/ Central European
A*23-B*44-DRB1*0701-DQB1*02g	1.2	Mediterranean/ European
A*02-B*50-DRB1*0701-DQB1*02h	1.2	Eurasiatic
A*02-B*35-DRB1*1401-DQB1*0503i	0.9	Mediterranean
A*24-B*35-DRB1*0403-DQB1*0302j	0.9	Eastern Mediterranean
A*02-B*18-DRB1*1104-DQB1*0301k	0.9	Mediterranean
A*33-B*14-DRB1*0102-DQB1*0501l	0.9	Mediterranean

HF: Haplotype frequency. a. This complete haplotype has not been found in any of the populations tested, however partial and generic typing B49-DR4 is present in French (HF: 1.0), Sardinians (HF: 4.1) and Spaniards (HF: 1.6). b and e. Extended haplotype (generic typing) has been found in Turks (HF: 0.9). Also, the partial haplotype B35-DR11-DQ7 is present in South African Negroid (HF: 2.1), Albanians (HF: 3.3), Armenians (HF: 5.0), Jews (HF: 6.2), Austrians (HF: 4.0), French (HF: 1.1), Germans (HF: 3.4), Greeks (HF: 2.6), Italians (HF: 6.8), Spaniards (HF: 1.3), Hungarians (HF: 3.9), Indians (HF: 3.1), Timorese (HF: 2.1) and Caucasoid Australians (HF: 3.7). c. Haplotype found in Armenians (2.1%) and Italians (0.7%). d. Also found in Germans (HF: 1.0) and Portuguese (HF: 2.3). f. Present in Austrians (HF: 2.7), Germans (HF: 1.4) and Italians (HF: 1.4). g. Mediterranean-Europeans. h. Present in Mongolians (HF: 3.2), Manchu (HF: 2.2), Spaniards (HF: 1.2) and Italians (HF: 0.5) (10turk). i. Extended haplotype found in Mexican Mestizos (HF: 2.9). Partially (B35-DR14) found in Italians (HF: 3.1), Greeks (HF: 1.7), and French (HF: 1.0). j. Partially (B35-DR4) found in Jews (HF: 6.0). k. This haplotype has been found in Albanians (3.9%), Italians (2.1%), Yugoslavs (3.5%), Turks (1.1%), Spaniards (1.1%) and Greeks (4.0%). l. Haplotype previously described as Mediterranean.

Other low frequency haplotypes present in Palestinians are also shared with Mediterraneans and central Europeans (A*01-B*08-DRB1*0301-DQB1*02, HF:0.6; A*03-B*07-DRB1*1501-DQB1*0602, HF: 0.6), Mediterraneans (A*02-B*35-DRB1*1104-DQB1*0301, HF:0.6; A*23-B*35-DRB1*1001-DQB1*0501, HF:0.6), Eurasiatics (A*02-B*08-DRB1*0301-DQB1*02, HF: 0.6), South West Asians (A*30-B*49-DRB1*1001-DQB1*0501, HF:0.6; A*02-B*49-DRB1*1001-DQB1*0501, HF:0.6; A*02-B*35-DRB1*0403-DQB1*0302, HF: 0.6), African Blacks (A*02-B*42-DRB1*0302, HF:0.6). Also, probably autochthonous A*02-B*50-DRB1*0402-DQB1*0302 (HF:0.6) haplotype has been found. Comparisons were made by using references [3,8,16-21,27-29]

cultural importance of this input is for constructing the classical Hellenistic culture. The reason why a sub-Saharan admixture is not seen in Crete is unclear but may be related to the influential and strong Minoan empire, which hindered foreigners establishment if the African invasion occurred in Minoan times [19, 20].

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REFERENCES

1. Dausset J, Colombani J: Histocompatibility Testing 1972. Copenhagen, Munksgaard, 1972.
2. Imanishi T, Wakisaka A, Gojorobi T: Genetic relationships among various human populations indicated by MHC polymorphisms. In Tsuji K, Aizawa M, Sasazuki T (eds): HLA 1991. Vol 1. Oxford, Oxford University Press, 627-32, 1992.
3. Clayton J, Lonjou C: Allele and Haplotype frequencies for HLA loci in various ethnic groups. In Charron D (ed): Genetic diversity of HLA, Functional and Medical Implications. Vol 1. Paris, EDK, 665-820, 1997.
4. Encyclopaedia Britannica (1999) Sutton, Surney: Encyclopaedia Britannica International Ltd.
5. Kienitz FK: Volker imm schatten. Die gegenspieter der Griechen und Römer. Munchen, Beck'sche Verlagsbuchhandlung, 1981.
6. Kuhrt A: The ancient Near East (3000-330 BC). Vol II. Barcelona, Editorial Critica, 2001.
7. Biblia de Jerusalén. Desclee de Brouwer (ed): Bilbao, Spain, 1998.
8. Martínez-Laso J, Gazit E, Gómez-Casado E, Morales P, Martinez-Quiles N, Alvarez M, Martin-Villa JM, Fernandez V, Arnaiz-Villena A: HLA DR and DQ polymorphism in Ashkenazi and non-Ashkenazi Jews: comparison with other Mediterraneans. Tissue Antigens 47: 63, 1996.
9. Sellier J, Sellier A: Atlas des Peuples d'Orient. Paris, Editions La Dècouverte, 1993.
10. Gonem A: The encyclopaedia of the peoples of the world. Jerusalem, Publishing House Ltd, 143-5, 1996.
11. El Estado del Mundo, 2000. Anuario geopolítico. Madrid, Akal Editions, 2000.
12. Arnaiz-Villena A, Timón M, Corell A, Pérez-Aciego P, Martín-Villa JM, Regueiro JR: Primary immunodeficiency caused by mutations in the gene

encoding the CD3-γ subunit of the T-lymphocyte receptor. N Eng J Med 327:529, 1992.

13. Excoffier L, Slatkin M: Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. Mol Biol Evol 12:921, 1995.
14. Imanishi T, Akaza T, Kimura A, Tokunaga K, Gojorobi T: Estimation of allele and haplotype frequencies for HLA and complement loci. In Tsuji K, Aizawa M, Sasazuki T (eds): HLA 1991. Vol I. Oxford, Oxford University Press, 76-9, 1992.
15. Mattiuz PL, Ihde D, Piazza A, Ceppelini R, Wodmer WF. Histocompatibility Testing 1970. Copenhagen, Munksgaard, 193-206, 1970
16. Imanishi T, Akaza T, Kimura A, Tokunaga K, Gojobori T: Allele and haplotype frequencies for HLA and complement loci in various ethnic groups. In Tsuji K, Aizawa M, Sasazuki T (eds): HLA 1991. Vol 1. Oxford: Oxford University Press, 1065-220, 1992.
17. Arnaiz-Villena A, Benmamar D, Álvarez M, Díaz-Campos N, Varela P, Gomez-Casado E, Martinez-Laso J: HLA allele and haplotype frequencies in Algerians. Relatedness to Spaniards and Basques. Hum Immunol 43:259, 1995.
18. Arnaiz-Villena A, Martínez-Laso J, Gómez-Casado E, Díaz-Campos N, Santos P, Martinho A, Breda-Coimbra H: Relatedness among Basques, Portuguese, Spaniards, and Algerian studied by HLA allelic frequencies and haplotypes. Immunogenetics 47:37, 1997.
19. Arnaiz-Villena A, Iliakis P, González-Hevilla M, Longás J, Gomez-Casado E, Sfyridaki K, Trapaga J, Silvera-Redondo C, Matsouka C, Martínez-Laso J: The origin of Cretan population as determined by characterization of HLA alleles. Tissue Antigens 53:213, 1999.
20. Arnaiz-Villena A, Dimitroski K, Pacho A, Moscoso J, Gomez-Casado E, Silvera C, Varela P, Martinez-Laso J: HLA genes in Macedonians and the sub-Saharan origin of the Greeks. Tissue Antigens 57:118, 2001.
21. Arnaiz-Villena A, Carin M, Bendikuze N, Gomez-Casado E, Moscoso J, Silvera C, Pacho A, Allende L, Guillén J, Martinez-Laso J: HLA alleles and haplotypes in the Turkish population: relatedness to Kurds, Armenians and other Mediterraneans. Tissue Antigens 57:308**,** 2001.
22. Saitou N, Nei M: The neighbor-joining method: a new method for reconstructing phylogenetic trees. Mol Biol Evol 4:406, 1987.
23. Nei M: Genetic distances between populations. Am Nat: 106:283, 1972.
24. Nei M: Analysis of gene diversity in subdivided populations. Proc Natl Acad Sci USA 70:3321, 1973.
25. Nei M, Tajima F, Tateno Y: Accuracy of estimated phylogenetic trees from molecular data II. Gene frequency data. J Mol Evol 19:153, 1983.
26. Young FW, Bann CM: A Visual Statistics system. In Stine RA & Fox J (eds): Statistical Computing Environments for Social Researchers. New York, Sage publications, 207-36, 1996.
27. Martínez-Laso J, De Juan D, Martínez-Quiles N, Gómez-Casado E, Cuadrado E, Arnaiz-Villena A: The contribution of the HLA-A, -B, -C and -DR, -DQ DNA typing to the study of the origins of Spaniards and Basques. Tissue Antigens: 45:237, 1995.
28. Gomez-Casado E, del Moral P, Martinez-Laso J, García-Gómez A, Allende L, Silvera-Redondo C, Longas J, González-Hevilla M, Kandil M, Zamora J, Arnaiz-Villena A: HLA genes in Arabic-speaking Moroccans: close relatedness to Berbers and Iberians. Tissue Antigens 55:239, 2000.
29. Bias W, Gazit E: 12th International Histocompatibility Workshop: Anthropology SWAS regional report. In Charron D (ed): Genetic diversity of HLA, Functional and Medical Implications. Vol 1. Paris, EDK, 353-363, 1997.
30. Arnaiz-Villena A, Martinez-Laso J, Alonso-García J: The correlation between languages and genes: the usko-Mediterranean peoples. Human Immunol (This issue)
31. Arnaiz-Villena A, Alonso-Garcia J: The Usko-Mediterranean languages. In Arnaiz-Villena A (ed): Prehistoric Iberia: Genetics, Anthropology and Linguistics. New York, Kluwer Academic-Plenum Publishers, 2000.
32. Arnaiz-Villena A, Martinez-Laso J, Alonso-Garcia A. Iberia: Population genetics, Anthropology, and linguistics. Hum Biol 71:725, 1999.
33. Herodotus: History. Madrid, Ed. Gredos, 1989.
34. Arnaiz-Villena A, Alonso-García J: El origen de los Vascos y otros pueblos Mediterraneos. Madrid, Editorial Complutense SA, 1998.
35. Arnaiz-Villena A, Alonso-García J: Minoicos, Cretenses y Vascos. Un estudio genético y lingüístico. Madrid, Editorial Complutense SA, 1999.
36. Arnaiz-Villena A, Alonso-García J: Egipcios, Bereberes, Guanches y Vascos. Madrid, Editorial Complutense SA, 2000.
37. Grollemberg LH: The Penguin shorter Atlas of the Bible. New York, Penguin Books Ltd, 1978.
38 Izaabel H, Garchon HJ, Caillat-Zucman S, Beaurain G, Akhayat O, Bach JF, Sanchez-Mazas A: HLA class II DNA polymorphism in a Moroccan population from the Souss, Agadir area. Tissue Antigens 51: 106, 1998.
39. Roitberg-Tambur A, Witt CS, Friedmann A, Safirman C, Sherman L, Battat S, Nelken D, Brautbar C: Comparative analysis of HLA polymorphism at the serologic and molecular level in Moroccan and Ashkenazi Jews. Tissue Antigens 46: 104, 1995.
40. Mehra NK, Rajalingam R, Kanga U, McEnemy L, Cullen C, Agarwal S, Middleton D, Pollack MS, Amirzargar A, Singal DP: Genetic diversity of HLA in the populations of India, Sri Lanka and Iran. In Charron D (ed): *Genetic diversity of HLA, Funcional and Medical Implications*. Vol 1. Paris, EDK, 314-20, 1997.