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The Investigation of the Evolutionary History of the Omani Population by Analysis of HLA Class I Polymorphism

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ABSTRACT The HLA polymorphism is a useful way to investigate the relatedness between human ethnic groups. This work aimed to study the relatedness of *Omanis with other modern ethnic groups using the HLA class I system polymorphism. The study enrolled 259* healthy and unrelated individuals who were randomly selected from the Omani population. Genotyping of HLA-A and -B loci was carried out by the molecular approach for all subjects. The HLA A and B allele frequencies were estimated by the maximum-likelihood rule. The interethnic analysis was performed using genetic distances measurements, Neighbour-Joining dendrograms and extended haplotypes analysis. The HLA allele analysis showed the presence of 16 variants at the A locus and 27 variants at the B locus. Statistically, the most frequent alleles were: HLA-A*02 (19.9%) and -B*35 (15.3%); and the most frequent HLA-A_B haplotype was: A*02_B*51 (5.6%). When compared to others ethnic groups, the Omanis showed a genetic relatedness to the Mediterranean and West-Asian peoples. The relatedness between Omani, Mediterranean and West-Asian population might be explained by several historic and socio-geographic factors if we flashback on the long history of the Omani population.

INTRODUCTION

Analyzing HLA polymorphism is a useful way to investigate the ethnic origin of human groups and to confirm cultural and linguistic studies. In fact, it has been demonstrated that HLA alleles and haplotypes distribution differ between ethnic groups and correlate with geographically related populations (Buhler and Sanchez-Mazas 2006). In this regard, it has been reported that gene flow between populations may be measured using the corresponding genetic distances estimated from HLA allele frequencies (Imanishi et al. 1992; Clayton and Lonjou 1997; Simoni et al. 1999). This is a quantitative measure of genetic divergence between two HLA loci giving a relative estimate of the time that has passed since two populations existed as a single panmictic population.

The Omani population is an Arabic population occupying the south eastern corner of the Arabian Peninsula and constitutes a very interesting model for investigating the dynamism and the evolution of human groups because of its long history. As reported by Paul Lunde in "Oman: A history", the coast of Oman was occupied by Persians early in history (Lunde 1983). In fact, from 6th to 4th century BC, Achaemenid, an Iranian dynasty, controlled and influenced the Omani peninsula. It has been reported that this control was most likely exerted from a coastal centre such as Sohar. The Persian control was extended also for 10 centuries until the arrival of Islam (from 3rd century BC to 7th century AD) and exerted by two other Iranian dynasties, the Parthians and the Sassanids. Oman territories *have experienced also the arrival of* tribes from Marib (Yemen) during the pre-Islamic time in a strategy to control the lucrative incense trade (Stewart 1978). With the advent of Islam, the Omani population was enriched with others tribes especially clans who fled south following the battle of Siffin in 657 and Ottomans who set out to relieve Muscat from Portuguese (Lunde

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1983). Thus, it appears clearly that Omanis are in regular contact with other ethnic groups during all ages that have led to heterogeneity of this population especially with interethnic marriages.

To date, few studies investigating the origin of Omanis have been published but none has used the HLA genetic distance method. Consequently, we decided to conduct a population genetic study using this approach to address this question. This work may help to more investigate the relatedness between Omanis and others middle east populations. Furthermore, such study could be helpful in making an Arabic HLA database that can be useful in clinical practices especially in *bone marrow* (BM) and solid organ transplantation (SOT) area.

METHODOLOGY

Informed consent was obtained from all participants, and approval was obtained from the ethical committee for scientific and medical research of the College of Medicine and Health Sciences at the University of Sultan Qaboos (Sultanate of Oman) for performing this study.

Human Samples

A total of 259 healthy and unrelated individuals were randomly selected from the Omani population. The origin of other populations used for interethnic comparison is detailed in Table 1.

Table 1: Populations used in this work for interethnic analysis (Gonzalez-Galarza et al. 2011).

N°	*Population*	*Sample size*
1	Oman	259 (*Present Study*)
2	Portugal Center	50
3	Spain-MM (Majorca and Minorca)	90
4	Iran Baloch	100
5	Tunisia-3 (Population 3)	104
6	Morocco	96
7	Saudi Arabia-GH (Guraiat and Hail)	213
8	Palestine Gaza	165
9	Albania	160
10	France Rennes-3 (Population 3)	200
11	Greece Crete	135
12	India New Delhi	71
13	Pakistan Baloch	66
14	Turkey-2 (Population 2)	228
15	Bangladesh-DB (Dhaka Bangalee)	141
16	Malaysia-2 (Population 2)	62
17	Philippines Ivatan	50

Molecular HLA Class I Typing and Haplotype Assignment

HLA-A and –B molecular genotyping was carried out using the PCR-SSP method according to manufacturer's specifications (Dynal Allset Gold SSP, Life Technologies Corp.)

Statistical Analysis

HLA-A/B allele and haplotype frequencies; and relative linkage disequilibrium (RLD or D') between these loci were calculated by applying the expectation–maximization (EM) algorithm (Arlequin program V3.5.12) (Excoffier and Lischer 2010). Standard deviations (SD) were obtained by a bootstrap procedure (Efron 1982). Phylogenetic tree (dendrogram) was constructed with allele frequencies by applying the Neighbor-Joining (NJ) method with the standard genetic distances (SGD) (Saito and Nei 1987; Nei 1972), using the Dispan software which contains the GNKDST and TREEVIEW application (Nei 1973; Nei et al. 1983).

RESULTS

HLA Class I Allele Frequencies

The allele analysis showed the presence of 16 variants at the HLA-A locus of which A*02, A*11 and A*32 were the most frequent in Omanis (Table 2). Except the A*02 allele which is very frequent in all populations, A*11 variant is a common allele among the Southeast Asian peoples such as in Bangladesh DB(15.6%), China YPN (38%), India KHP (53.1%), Malaysia NSM (28%), Pakistan Baloch (22.2%), Thailand Northeast (27.1%); while A*32 appears a more frequent allele in Mediterraneans such as in France Southeast (7.2%), Gaza (6%), Macedonia (4.9%), Morrocco (4.1%), Spain NC (6%) and Tunisia (6.6%) (Clayton and Lonjou 1997).

For the HLA-B locus, 27 alleles were detected in which B*35 and B*51 appear to be the most frequent alleles in Omanis (Table 2). HLA-B*35 is a very frequent allele in Amerindians such as in Guatemalans "Mayan" (45.9%), Mexicans "Huasteca Region Teenek" (38.9%), Mexicans "Nahuas " (29.8%) and Argentineans "Salta Wichi" (36.8%), whereas a very lower frequency of this allele was reported in several Southeast Asian populations (Gonzalez-Galarza et al. 2011). How

Table 2: HLA-A and -B allele frequencies estimated under unknown gametic phase in the Omani population

No.	*A Locus*	*Allele frequency*	*S.D.*	*B Locus*	*Allele frequency*	*S.D.*
1	A*01	0.058	0.010	B*07	0.031	0.007
2	A*02	0.199	0.018	B*08	0.093	0.013
3	A*03	0.050	0.009	B*13	0.012	0.005
4	A*11	0.108	0.014	B*14	0.015	0.006
5	A*23	0.023	0.007	B*15	0.060	0.011
6	A*24	0.081	0.012	B*18	0.042	0.009
7	A*26	0.087	0.012	B*27	0.004	0.003
8	A*29	0.023	0.007	B*35	0.153	0.016
9	A*30	0.075	0.012	B*37	0.008	0.004
10	A*31	0.048	0.009	B*38	0.014	0.005
11	A*32	0.091	0.011	B*39	0.019	0.006
12	A*33	0.058	0.010	B*40	0.064	0.011
13	A*36	0.006	0.003	B*41	0.012	0.005
14	A*66	0.008	0.004	B*42	0.017	0.006
15	A*68	0.071	0.012	B*44	0.021	0.006
16	A*74	0.014	0.005	B*45	0.014	0.005
17				B*47	0.004	0.003
18				B*49	0.008	0.004
19				B*50	0.042	0.009
20				B*51	0.147	0.015
21				B*52	0.060	0.010
22				B*53	0.015	0.006
23				B*55	0.017	0.006
24				B*57	0.019	0.006
25				B*58	0.091	0.014
26				B*73	0.012	0.005
27				B*81	0.008	0.004

ever, HLA-B*51 is predominant in Caucasoid such as in Bulgarians (20.9%), Albanians (17.2%), Macedonians "population 4" (15.3%).

Omani HLA class I allele frequencies were compared with other Mediterranean and Asian populations frequencies in order to investigate the relatedness between these peoples (Fig. 1). In this analysis, we used only HLA-A allele frequencies because some of the populations included in this comparison lacked some HLA-B data. The phylogenetic analysis showed that Omanis are closer to Mediterranean and Arabic peoples than to Asian and Southeast Asian peoples, which was more evident in Table 3 where Omanis-Iranians Baloch, Omanis-Tunisians, Omanis-Spanish, Omanis-Portuguese and Omanis-Moroccans show a closest genetic distance (SGD).

HLA-A_B Haplotype Frequencies and Linkage Disequilibria

The statistical analysis showed that the most dominant HLA-A_B haplotypes in Omanis are HLA-A*02_B*51 (5.6%) and HLA-A*02_B*35 (5%), but the most dominant HLA-A_B haplotypes with linkage disequilibrium are HLA-A*26_B*08 and HLA-A*11_B*40 (Table 4). HLA-A*26_B*08 was detected in 5.4% of Pakistan "Baloch" and in 1.5 % of Guinea Bissau

Table 3: Standard genetic distances (SGD) between Omanis and other populations

No.	*Population*	*HLA-A (SGD)*
1	Iran Baloch	0.003
2	Tunisia-3	0.004
3	Spain-MM	0.018
4	Portugal Centre	0.052
5	Morocco	0.069
6	India New Delhi	0.070
7	Pakistan Baloch	0.076
8	Albania	0.076
9	Palestine Gaza	0.085
10	Saudi Arabia-GH	0.096
11	Greece Crete	0.097
12	Turkey-2	0.134
13	France Rennes-3	0.135
14	Bangladesh-DB	0.167
15	Malaysia-2	0.310
16	Philippines Ivatan	0.387

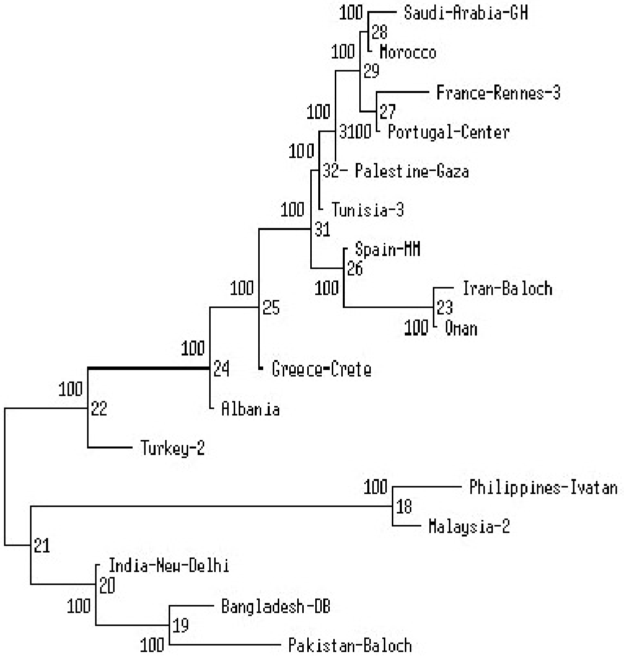

Fig. 1. Neighbour-joining dendrogram showing relatedness between Omanis and other populations. Standard genetic distances (SGD) were calculated by using HLA-A allele frequencies. Data from other populations were taken from references detailed in Table 1. Bootstrap values from 1000 replicates are shown.

Table 4: HLA-A_B haplotype frequencies and linkage disequilibrium values (|*D'*|)

	Major HLA-A_B haplotypes			*Most linked A_B loci (Only |D'|> 0.400)*			
S.No	*A_B Loci*	*Frequency*	*S.D.*	*A_B Loci*	*Frequency*	*S.D.%*	*D'%*
1	A*01_B*51	0.013	0.006	A*11_B*40	0.030	0.008	0.403
2	A*01_B*58	0.023	0.007	A*11_B*57	0.009	0.005	0.419
3	A*11_B*18	0.014	0.006	A*26_B*44	0.010	0.005	0.403
4	A*11_B*35	0.014	0.006	A*26_B*08	0.040	0.009	0.406
5	A*11_B*40	0.030	0.008	A*03_B*27	0.002	0.002	0.474
6	A*11_B*52	0.017	0.006	A*30_B*42	0.015	0.006	0.880
7	A*02_B*35	0.050	0.011	A*31_B*39	0.013	0.005	0.683
8	A*02_B*40	0.016	0.006	A*32_B*47	0.002	0.002	0.450
9	A*02_B*50	0.021	0.007	A*33_B*27	0.002	0.002	0.469
10	A*02_B*51	0.056	0.011	A*33_B*81	0.004	0.003	0.469
11	A*02_B*58	0.014	0.006	A*66_B*41	0.006	0.003	0.747
12	A*24_B*35	0.020	0.007	A*74_B*15	0.008	0.004	0.544
13	A*24_B*51	0.013	0.006				
14	A*24_B*08	0.014	0.006				
15	A*26_B*35	0.017	0.006				
16	A*26_B*08	0.040	0.009				
17	A*30_B*15	0.015	0.006				
18	A*30_B*35	0.012	0.005				
19	A*30_B*42	0.015	0.006				
20	A*31_B*39	0.013	0.005				
21	A*32_B*18	0.015	0.006				
22	A*32_B*35	0.027	0.008				
23	A*32_B*51	0.014	0.007				
24	A*32_B*52	0.019	0.006				
25	A*33_B*51	0.010	0.005				

and “Baloch” peoples with frequencies respectively of 10% and 9.5% (Gonzalez-Galarza et al. 2011). The very high linkage disequilibrium value observed in this study was $|D'|= 0.88$ and corresponds to HLA-A*30_B*42 haplotype which is detected in 1.5% of Omanis (Table 4). This haplotype was also detected in USA-Asian/Hispanic peoples with a frequency of 3% (Gonzalez-Galarza et al. 2011).

DISCUSSION

Historic nature of the human is characterized by his dynamism and movement for searching natural resources for his life. In fact, peoples have colonized fertile lands, coasts and main trading routes especially linking the east of the globe to the west. In this regard, Omani territories and coasts have represented from antiquity a principal trading route and Oman has experienced the arrival and the installation of peoples from various ethnicities. Thus, we decided to investigate the relatedness of Omanis with other modern ethnic groups using the HLA class I system polymorphism.

The HLA class I allele analysis showed that the frequent HLA-A variants in Omanis are those that are common in Arabs (Palestinians, Saudis and Moroccans) and Mediterranean’s (Grecians, Portuguese and French) especially the HLA-A*02 and HLA-A*32 variants. The same result was also observed when analysing the HLA-B locus except the HLA-B*35 which is very frequent in Amerindians. Thus, it appears clearly that there is an HLA allele admixture between Omanis and Mediterranean-West Asian peoples. The most surprising result was that when analysing HLA class I haplotype we revealed that the predominant haplotypes with significant linkage disequilibrium in Omanis e.g. HLA-A*11_B*40 and HLA-A*26_B*08 are those predominant in the Pakistani “Baloch” group. However, the analysis of others haplotypes revealed that the predominant haplotype in Omanis e.g. HLA-A*02_B*51 is a common haplotype between Mexicans, Portuguese, Moroccans, Tunisians, Romanians and Pakistani “Brahui”. So, we believe that these findings provide evidence *that Omanis are close to* Mediterranean and West-Asian populations which appeared clearly in the phylogenetic analysis (dendrogram) while we think that is not very informative and discriminating. This fact might be explained by several historic and socio-geographic factors if we flashback on the long history of this region.

The relatedness of Omanis to Mediterranean and West-Asian populations was not surprising in view of the above cited reasons. In fact, the genetic overlapping between Omanis and West-Asian peoples is likely to be correlated with interethnic marriages during the Persian domination of the coast of Oman early in history. *The same theory may* also be valid to explain the relatedness of Omanis to Mediterranean peoples and we think that some Mediterranean groups who came to Oman for trade were finally installed. This vision may be reinforced by the importance of Oman territories as an antique economic and military area. In fact, Oman is located in a strategic region that links the ancient *Fertile Crescent or* “The Cradle of Civilization” to the Indian Ocean area and it is in the same time a very appropriate location to control sea incense trade routes between the Arabian Gulf, Gulf of Oman and Indian Ocean. So, it is quite normal to be colonized by major forces such as Persians followed by tribes of Marib, Portuguese and Ottomans that leaded to an admixture of the Omani’s genetic patrimony.

To our knowledge, this is the first published study investigating the relatedness between Omanis and other populations using the HLA system. In this investigation, the distribution of HLA class I alleles and haplotypes among Omanis suggests influence from several ethnic groups and that Omanis appear to be related to Arabs, Mediterranean’s and West-Asians particularly Baloch group. Our study results provide information that may be used for anthropological studies and in analyzing disease susceptibility and organ/*bone marrow* transplantation.

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