Genetic Variation in the Population of Ibiza (Spain): Genetic Structure, Geography, and Language

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Abstract A sample of 203 individuals from Ibiza (Balearic Islands, Spain) were tested for blood group and serum protein genetic variation and compared with other circum-Mediterranean populations. Allele frequencies were calculated for the following blood group and serum systems: ABO, Rh, MNSs, P, Lewis, Duffy, Kell, ORM, GC, TF, PI, and HP. The allele frequencies from Ibiza were compared with those from other Balearic Islands (Majorca and Minorca) and with related European and North African groups using an assortment of analytical methods (genetic distances, *R* matrix analysis, and Mantel tests). *R* matrix analysis revealed that Ibiza is genetically different from the other Balearic populations and, because of gene flow from Spain, clusters with European groups. The level of genetic microdifferentiation of the Mediterranean populations, measured by R_{ST} (average of the *R* matrix diagonal elements, r_{ii}), is 0.028. An examination of the relationship between genetic, geographic, and linguistic distances by Mantel tests revealed that genetic distances are significantly correlated with linguistic distances, whereas the genetic distances are not significantly correlated with geographic distances. The plot of mean per locus heterozygosity versus the genetic distance from the centroid of distribution revealed that all three Balearic Islands have experienced considerable gene flow but that Ibiza has been most affected by the action of stochastic processes.

Island populations have been of great fascination to population geneticists and biological anthropologists because these reproductively isolated and often small human aggregates offer an opportunity to investigate the effects of stochastic processes and unique historical events. For example, the research on the population of Tristan da Cunha by Roberts (1968) yielded considerable

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insight into the evolutionary effects of unique historical events on subsequent generations. Similarly, the influence of geography on the genetic structure of the Åland Islands was revealed using island populations (Mielke et al. 1982). More recently, Crawford et al. (1995) demonstrated the effects of the interaction of religion, economics, and geography on the genetic structure of the island isolates of Newfoundland. In contrast to these geographic isolates, Ibiza and the other two Balearic islands were located on the crossroads of historical population movements in the circum-Mediterranean region. They offer an opportunity to observe the interactions between successive migrations and the actions of stochastic processes on a small founding population.

Population

Ibiza is a small island in the Mediterranean Sea located approximately 70 km from Spain and 100 km from Majorca (Figure 1). Ibiza is the smallest of the three main Balearic Islands with an area of 567 km^2, compared with Majorca (3640 km^2) and Minorca (702 km^2). Ibiza differs from the other two islands in landscape, vegetation, and especially the origins of founding settlements.

There is no archeological evidence for human habitation on Ibiza before the arrival of the Carthaginians in 654 B.C. If the island was occupied during the prehistoric period, its residents failed to leave evidence of the "talaiotic" (stone builder) culture that is prominent in both Majorca and Minorca. The Carthaginians remained in Ibiza for at least five centuries. They founded the largest city, Ibusium (currently Ibiza), named after the Egyptian-Phoenician-Carthaginian god Bes. The Carthaginians were not restricted to coastal areas but also colonized the interior of the island.

Ibiza was annexed by the Roman Empire in 123 B.C. as part of a political pact. Apparently, the Romans failed to occupy Ibiza, as evidenced by the absence of any Roman remains on the island. The Balearic archipelago came under Moslem domination from the seventh to the twelfth century, leaving behind both cultural and possibly biological influences. In A.D. 1229 the Catalans expanded into the Balearic archipelago from what is now Spain, first with an invasion of Majorca and then in 1235 by the occupation of Ibiza.

The autochthonous population of Ibiza has grown from approximately 3,000 persons in 1392 to 9,596 inhabitants in 1652 to approximately 40,000 people in 1990. In 1990 the total population of Ibiza was 80,538, but only 50% of these inhabitants were autochthonous.

During the last seven centuries the Ibiza population has been reproductively isolated and thus received little gene flow from outside. This apparent reproductive isolation was disturbed by a 1970s tourist influx that promoted immigration from mainland Spain and doubled the total population. The small size of the autochthonous population and its reproductive isolation resulted

Figure 1. Location of Ibiza, Minorca, and Majorca in the Mediterranean Sea.

in a moderate incidence of consanguineous marriages (Valls 1969). The percentage of consanguineous unions varies from 1% to 16% in parishes scattered throughout the island with an average of 5.59% for the entire island. Wright's *F* inbreeding coefficient for Ibiza was computed to be 0.0019 (Valls 1969).

The history of Ibiza, which can be characterized by its gene flow followed by reproductive isolation, is reflected in the gene pool of the contemporary population. Thus a genetic analysis of Ibiza and comparison with other human settlements of the Mediterranean should contribute much to our understanding of Ibiza's history and the actions of evolutionary processes.

To date, the population of Ibiza has been characterized genetically by a few blood groups (Mourant et al. 1976) and erythrocytic enzymes (Miguel and Petitpierre 1989). The aims of this study were (1) to extend the genetic

characterization of the island population by testing for additional blood groups and serum proteins; (2) to compare the allelic frequencies observed in Ibiza with those of other circum-Mediterranean populations; (3) to measure any possible genetic differentiation of the Ibiza population from the other Balearic islands and the populations of mainland Spain and North Africa; (4) to estimate the differential contributions of European, Middle Eastern, and North African populations to contemporary Ibiza; and (5) to determine the relative roles of geography and linguistics in the migration patterns to Ibiza.

Materials and Methods

Blood Analysis. Blood samples from 203 individuals of the autochthonous population were collected in a local hospital in Ibiza city. These specimens were immediately shipped (at 4°C) to the Laboratory of Genetics in Palma, Majorca. For the ABO and Rh systems the sample size was larger, with data on 487 individuals. These additional samples were made available from an earlier investigation.

Blood grouping was done immediately upon receipt of the specimens, whereas the serum samples were kept frozen at −20°C and analyzed later. Blood groups were typed using the standard techniques recommended by the antiserum manufacturers (Behring and Marburg of Germany and Grifols of Barcelona, Spain).

Haptoglobins were typed by horizontal starch gel electrophoresis following the methods of Smithies et al. (1962). The systems GC, ORM, PI, and TF were typed by isoelectric focusing using the automated Phastsystem (Pharmacia, Uppsala, Sweden) on miniaturized gels in a pH gradient of 4.0–6.5. The separation was followed by immunofixation (GC and ORM) or by protein staining (PI and TF) using the methods of Carracedo et al. (1986), Moral (1987), and Montiel et al. (1988). Before TF and ORM typing, samples were treated with ferrous ammonium sulfate for TF typing, as described by Constans et al. (1980), or with neuraminidase for ORM typing (Carracedo et al. 1986).

Analytical Methods. Allele frequencies of 13 loci from 15 populations were used to construct a variance-covariance R matrix, which underwent principal components analysis (Harpending and Jenkins 1973). The average of the diagonal elements (r_{ii}) provides an estimate of R_{ST}, the equivalent of Wright's F_{ST} and Wahlund's F (Harpending and Jenkins 1973). The eigenvectors, scaled by the square roots of their respective eigenvalues, were plotted to produce genetic maps.

The allele frequencies used to construct the R matrix primarily came from a number of published compilations (Mourant et al. 1976; Roychoud-

hury and Nei 1988; Tills et al. 1983). Other recent sources of gene frequency data on Minorca, Majorca, and Ibiza are Miguel and Petitpierre (1989) and Moral (1987).

Matrices were constructed based on geographic, genetic, and linguistic distances. The geographic distances were measured in kilometers as straight-line distances (as the crow flies) between populations. Euclidean genetic distances were derived from the R matrix using the formula derived by Harpending and Jenkins (1973) for each pair of populations i and j:

$$d_{ij}^2 = r_{ii} + r_{jj} - 2r_{ij}. \tag{1}$$

Linguistic distances were based on a hierarchical classification, which permits the conversion of the order of relationships into scores or distances (Crawford and Duggirala 1992). Populations speaking different dialects of the same subgroup of languages were assigned a distance of 1. Populations speaking languages that belong to different subgroups within a given group of languages were assigned a distance of 2. A distance of 3 was assigned to populations speaking different groups of languages that are in a given subbranch. Languages that fall into different subbranches of a given branch are separated by a distance of 4. If the languages belong to two different branches within a subfamily, they are separated by a distance of 5. If the languages belong to two separate linguistic families, a distance of 6 is assigned. The scheme of Bec (1971) was used as the basis for the classification of the Romance languages.

To examine the interaction between genetic, geographic, and linguistic distance matrices, we computed normalized product-moment correlations, partial correlations, and multiple correlations using the MANTEL program (Relethford 1990). Mantel's (1967) permutation procedure, based on a general regression approach, is a valid tool for measuring the correlation or association between the elements of any two matrices. As such, the correspondence between the two given matrices A and B can be measured by using the Mantel test statistic (Z):

$$Z_{AB} = \sum_{ij} A_{ij}B_{ij}, \tag{2}$$

where Z_{AB} is the sum of cross-products between A_{ij} and B_{ij}, the elements of row i and column j of matrices A and B. Because Z_{AB} is an unnormalized correlation coefficient, it has to be normalized into a product-moment correlation coefficient that ranges from -1 to $+1$ (Dow and Cheverud 1985; Smouse et al. 1986; Dow et al. 1987). In this method a sampling distribution of the Mantel statistic is generated through repeated simultaneous permutations of the rows and columns of one of the matrices. The significance level is obtained as the proportion of the generated Mantel statistic (Z_{AB}) that is greater than or equal to the observed correlation (Relethford 1988).

Distance measures were compared by computing Pearson's product-moment correlations between the two given matrices, and the significance levels were ascertained using Mantel's permutation test (Mantel 1967).

The partial correlation approach was based on the regression of each element of the two distance matrices on a control matrix. Therefore partial correlation is the correlation between the corresponding elements in the two residual matrices (R_1 and R_2) that remain after the removal of the effects of the control matrix (Dow et al. 1987). Given three distance matrices A (genetic distance), B (geographic distance), and C (linguistic distance), three partial correlation coefficients, $r_{AB(C)}$, $r_{AC(B)}$, and $r_{BC(A)}$, were obtained by using a least-squares regression method, wherein the partial correlation $r_{AB(C)}$ indicates the association between matrices A and B while keeping the C matrix constant (Dow and Cheverud 1985; Dow et al. 1987). Significance levels for the partial correlations between the dependent distance matrix (genetic distance) and one of the two independent matrices (geographic or linguistic distance) were obtained by controlling the effects of one of the two independent matrices. Therefore the association between the genetic and geographic distances was exclusively measured by keeping the linguistic distance constant.

Multiple correlations yield the relative effects of the two independent matrices (B and C) on the dependent matrix (A). In this method the expected values are computed through multiple regression analysis. The product-moment correlations are computed between the expected values and the observed values of the dependent variable (Relethford 1990).

Linkage disequilibria were calculated using the programs LD79.FOR and LD86.FOR (Weir 1990).

Results

Phenotype numbers and allele frequencies of blood groups and serum proteins are summarized in Tables 1 and 2. With the exception of the Duffy system, all loci were in Hardy-Weinberg equilibrium. The Duffy system showed a significant excess of homozygotes ($\chi^2 = 5.5$, d.f. $= 1, p < 0.05$). A slight excess of homozygotes was observed in five of seven systems (MN, Ss, ORM, TF, and HP). However, a one-tailed sign test was carried out and showed no significance ($p = 0.14$). This slight excess of homozygotes may be the result of inbreeding (Valls 1969). The significant excess of homozygotes at the Duffy locus may be the result of selection for the FY silent allele, which is not detectable with a single antiserum. High prevalence of malaria on Ibiza could have acted as a selective agent.

MacArthur and Wilson (1967) hypothesized that populations living in reduced geographic areas have reduced levels of heterozygosity. Thus the lower heterozygosity in Ibiza may be attributed to gene frequency drift. To

Table 1. Distribution of Phenotypes and Gene Frequencies of Blood Groups in Ibiza

System	*Phenotype*	*N*	*Allele*	*Frequency*	χ^2	*d.f.*	*Significance*[a]
MNSs	M S	4	*M*	0.517 ± 0.029	0.0	1	n.s.
(n = 150)	M S,LS	11	*N*	0.483 ± 0.029			
	M LS	16	*S*	0.272 ± 0.028	3.1	1	n.s.
	M,N S	8	*LS*	0.728 ± 0.028			
	M,N S,LS	24					
	M,N LS	28	*MS*	0.180 ± 0.027	6.2	3	n.s.
	N S	1	*MLS*	0.316 ± 0.032			
	N S,LS	6	*NS*	0.093 ± 0.022			
	N LS	25	*NLS*	0.411 ± 0.034			
	M	9					
	M,N	15					
	N	3					
P	P1+	62	*P1*	0.234 ± 0.026			
(n = 150)	P1−	88	*P2* + *P*	0.766 ± 0.026			
Lewis	A	31	*Le*	0.569 ± 0.041			
(n = 124)	B	70	*le*	0.431 ± 0.041			
	−	23					
Duffy	B	74	*FY*A*	0.382 ± 0.027	5.5	1	$p < 0.05$
(n = 146)	A	21	*FY*B*	0.618 ± 0.027			
	A,B	51					
Kell	K+	16	*K*	0.055 ± 0.013			
(n = 150)	K−	134	K_c	0.945 ± 0.013			
ABO	O	286	*ABO*O*	0.786 ± 0.014			
(n = 487)	A	175	*ABO*A*	0.107 ± 0.014			
	B	20	*ABO*B*	0.107 ± 0.004			
	A,B	6					
Rh	D+	384	*D*	0.540 ± 0.020			
(n = 487)	D−	103	*d*	0.460 ± 0.020			

a. n.s. = not statistically significant.

test this hypothesis, we performed a correlation analysis between mean per locus heterozygosity and the logarithm of the geographic area using several Mediterranean islands. The mean heterozygosities of Alonissos (0.33), Ibiza (0.34), Minorca (0.35), Majorca (0.36), Sardinia (0.35), and Sicily (0.36) were regressed against area. The observed correlation (r = 0.485) was positive but not statistically significant. Ibiza, one of the smallest islands, had one of the lowest levels of heterozygosity. Thus the observed deficiency of heterozygotes should not be attributed to the island environment.

The allele frequencies for Ibiza were compared with data from other circum-Mediterranean populations (Mourant et al. 1976; Roychoudhury and Nei 1988; Tills et al. 1983; Alonso et al. 1990; Gamero et al. 1988; Sebentan and Sagisaka 1988). Based on its history, Ibiza is an admixed population of North African and European ancestry; therefore this population should exhibit

Table 2. Distribution of Phenotypes and Gene Frequencies of Serum Proteins in Ibiza

System	*Phenotype*	*N*	*Allele*	*Frequency*	χ^2	*d.f.*	*Significance*[a]
ORM	F1	59	*ORM*F1*	0.518 ± 0.025	3.3	1	n.s.
(*n* = 194)	F1,F2	1	*ORM*F2*	0.008 ± 0.004			
	F2	0	*ORM*S*	0.474 ± 0.025			
	F1,S	82					
	F2,S	2					
	S	50					
GC	1	92	*GC*1*	0.684 ± 0.023	0.05	1	n.s.
(*n* = 198)	1,2	87	*GC*2*	0.316 ± 0.023			
	2	19					
TF	C1	114	*TF*C1*	0.742 ± 0.020	1.6	1	n.s.
(*n* = 198)	C1,C2	55	*TF*C2*	0.210 ± 0.020			
	C2	11	*TF*C3*	0.020 ± 0.007			
	C1,C3	3	*TF*B*	0.028 ± 0.008			
	C2,C3	4					
	C3	0					
	C1,B	8					
	C2,B	2					
	C3,B	1					
	B	0					
PI	M1	121	*PI*M1*	0.793 ± 0.020	1.29	1	n.s.
(*n* = 198)	M1,M2	34	*PI*M2*	0.096 ± 0.014			
	M2	1	*PI*S*	0.103 ± 0.015			
	M1,S	35	*PI*Z*	0.008 ± 0.004			
	M2,S	2					
	S	2					
	M1,Z	3					
	M2,Z	0					
	S,Z	0					
	Z	0					
HP	1	30	*HP*1*	0.381 ± 0.024	0.13	1	n.s.
(*n* = 198)	1,2	91	*HP*2*	0.619 ± 0.024			
	2	77					

a. n.s. = not statistically significant.

intermediate frequencies of genetic markers compared with its parental populations. Some systems do indeed show frequencies that resemble North African and Middle Eastern populations. For example, the *FY*A* allele has a low frequency in North Africa and the Middle East (0.177–0.293) but a higher incidence in European populations (0.327–0.488). Ibiza exhibits the lowest *FY*A* frequency observed to date in Europe (0.319). The *TF*C2* allele has one of the highest values (0.210) in Europe, similar to values found in some North African populations (0.215). Populations of the Middle East have the highest frequency of the *TF*C2* allele (0.275). The *TF*C3* allele has a low

incidence in the Ibiza population, similar to the frequencies found in southern Spain and in North Africa.

Some systems indicate that Ibiza differs from European populations. For example, the frequency of the *MS* haplotype (0.180) is low for Europe but does not differ significantly from the frequency in Turkey (0.190), Sardinia (0.195), and Crete (0.190). In the Rh system the *D* allele has the lowest frequency (0.540) for Europe with the exception of the Basques (0.489). In the PI system the *PI*M2* allele frequency (0.096) is the lowest observed in Europe and other Mediterranean populations (0.140–0.200) but resembles the values seen in France (0.092) and Egypt (0.082). The *PI*S* allelic frequency is distributed along an east-west cline in the Mediterranean populations. The *P1* (P system) allele has a very low frequency in Ibiza (0.234), resembling the frequency for the population of Malta (0.290). The frequency of the *ABO*O* allele in the Ibiza population (0.766) is among the highest observed in the Mediterranean area, with only Sardinia (0.779) and Trentino, Italy (0.769), surpassing it. Although there is little comparative population data on the ORM system, Ibiza appears to have a low frequency of the *ORM*F1* allele. The frequencies of the other genetic markers studied in Ibiza are well within the ranges observed in Mediterranean populations.

The blood genetic data were tested for linkage disequilibria; however, no statistically significant values were observed.

In the principal components analysis plot of the *R* matrix, the first eigenvector (which accounts for 34.2% of the variance) separates the North African groups from the European populations (Figure 2). The second eigenvector (16.24% of the variance) distinguishes the Middle Eastern and Greek populations from Italian and Sardinian groups. Minorca and Majorca appear to cluster closely with southern Spain, Catalonia, and Corsica. Ibiza is intermediate between Spain, the other Balearic islands, and Sardinia. This plot is suggestive of Ibiza's uniqueness from Majorca and Minorca, thus reflecting the influence of unique historical events.

Figure 3 shows which alleles contributed to the dispersal of the populations in the previous two-dimensional gene map (Figure 2). Ibiza is distinguished from the other Balearic island populations on the basis of the frequencies of the *TF*C3* and *P2* + *p* alleles. The North African populations are distinguished from the European groups by the high incidence of *GC*1*, *FY*2* + *FY*3*, and *ACP*B* alleles.

The R_{ST} value for the Mediterranean populations, a measure of genetic heterogeneity, is relatively low, if viewed on a worldwide basis, but high for European populations (Jorde et al. 1982). The R_{ST} value of 0.028 is slightly lower than the values recorded for Australian aboriginal populations (0.04) and for East Highlands New Guineans (0.038). The European populations have values in the range 0.0002–0.0136 (Jorde et al. 1982).

The relationship between mean per locus heterozygosity *H* and distance from the centroid r_{ii} is shown in Figure 4. Ibiza exhibits both a high hetero-

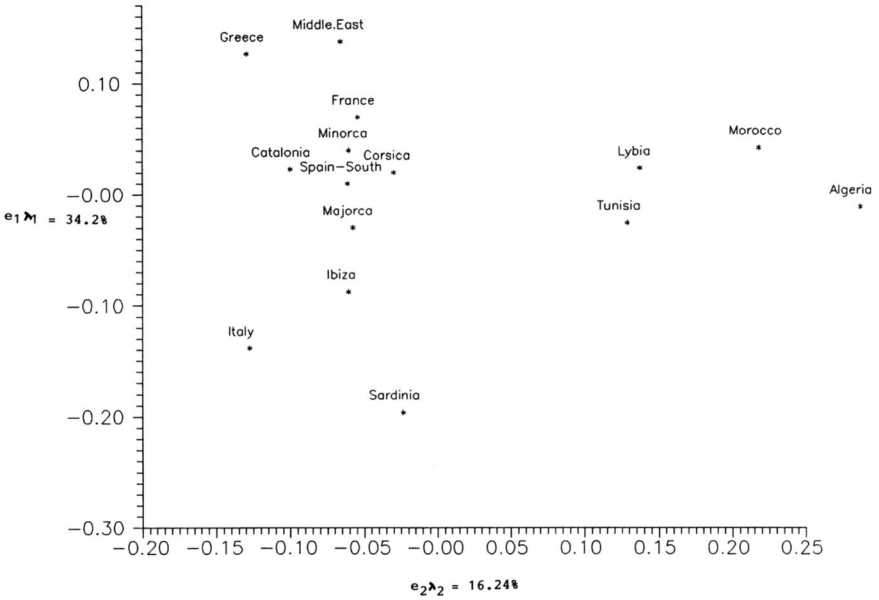

Figure 2. Least-squares reduction genetic map of 15 Mediterranean populations based on allele frequencies for the ABO, Rh, MNSs, Kell, P, FY, PGD, PGM, GC, ACP, HP, and TF loci. A total of 50.44% of the variance is explained by the plot of the first two eigenvectors.

zygosity (possibly reflecting the admixture of the founding populations) and relatively great distance from the centroid of distribution (most likely the result of stochastic processes). By far, the most isolated population appears to be the Algerian sample, which has a high distance from the centroid and a low heterozygosity.

Concordances between Distances. Table 3 summarizes the results of the pairwise Mantel tests. At the population level the product-moment correlations between two of the three distance matrix comparisons are statistically significant. A relationship exists between linguistic distance and both genetic and geographic distance, with a correlation between genetics and language of 0.152 ($p > 0.05$) and a correlation between geography and language of 0.178 ($p = 0.05$). Yet there is no apparent relationship between genetics and geography.

Partial correlations were made on genetic, geographic, and linguistic distance matrices. When either the language or geography were kept constant, there was no statistically significant association between genetics and geography or between genetics and language (Table 4).

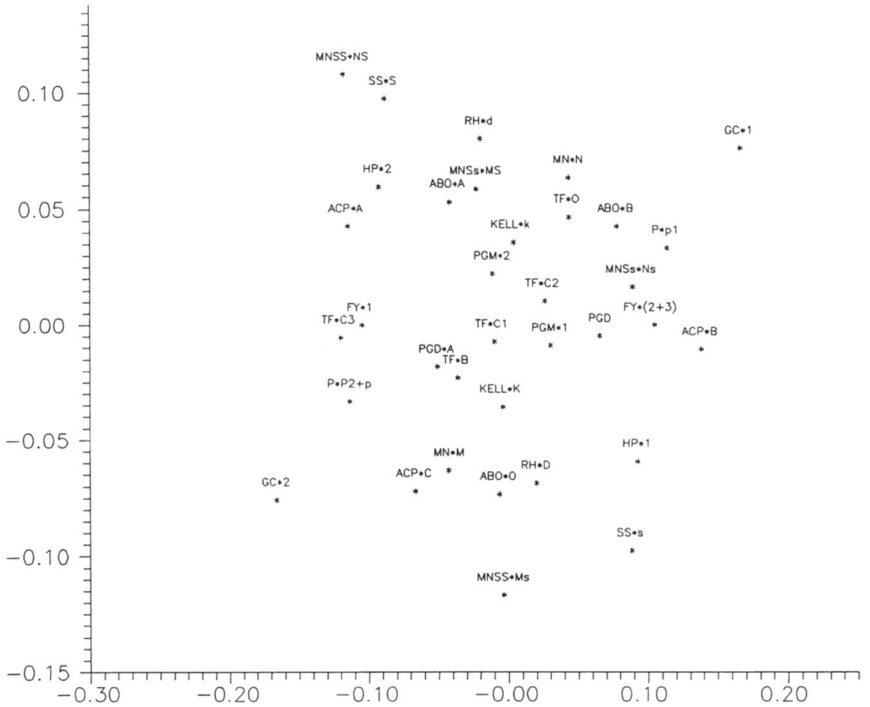

Figure 3. Least-squares reduction genetic map of the 35 alleles of the 12 loci corresponding to the map in Figure 2.

A multiple regression analysis of one distance matrix on the other two matrices also failed to indicate any statistically significant relationships between geography, genetics, and language (Table 5). Apparently, the effects of migration and conquest have swamped most of the effects of stochastic processes that under genetic and geographic isolation would accentuate differences between populations. The only statistically significant relationship, although marginal, exists between language and genetics and geography. Thus language serves as the best predictor of genetic variation in the Mediterranean populations.

Discussion

Our results indicate that genetic differences exist between Ibiza and the other main Balearic islands (Majorca and Minorca). These three populations have similar histories except for the Carthaginian original settlement of Ibiza. As a result, Ibiza has closer genetic affinities to the Middle East and North

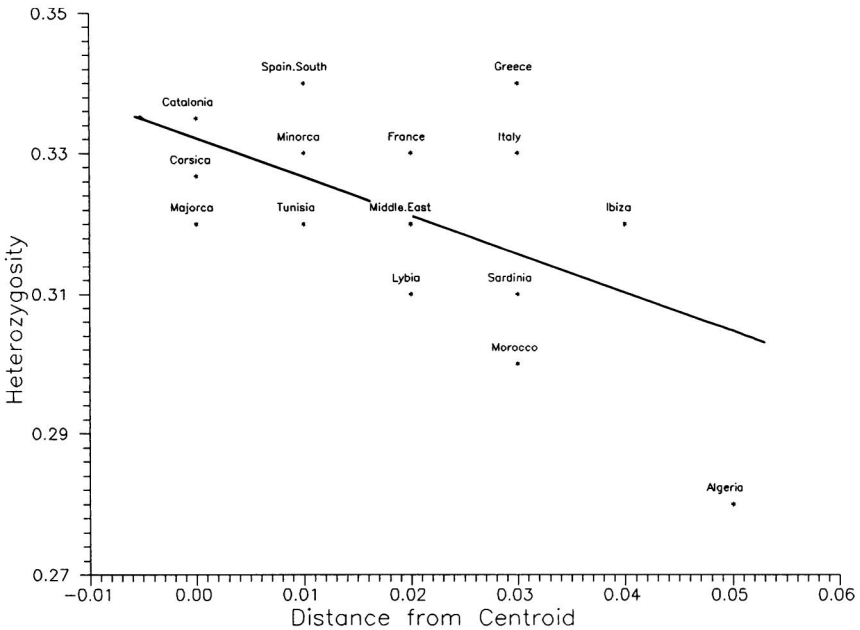

Figure 4. Plot of mean per locus heterozygosity H against distance from the centroid of distribution r_{ii} of the relationship matrix for 15 Mediterranean populations.

Table 3. Pearson's Product-Moment Correlations for Genetic (GEN), Geographic (GEOG), and Linguistic (LANG) Distance Matrix Comparisons among Ibiza and Other Mediterranean Populations

Test of Relationship	*Correlation*	*Significance* (p)
GEN*GEOG	0.119	0.127
GEN*LANG	0.152	0.068[a]
GEOG*LANG	0.178	0.058[b]

a. $p > 0.05$.
b. $p = 0.05$.

Table 4. Partial Correlation between Two Matrices While Controlling for the Third Matrix

Test of Relationship	*Correlation*	*Significance* (p)
GEN*GEOG.LANG	0.095	0.189
GEN*LANG.GEOG	0.132	0.112

Table 5. Multiple Correlation Coefficients of One Distance Matrix on Two Other Matrices

Test of Relationship	*Multiple Correlation*	*Significance (p)*
GEN*GEOG.LANG	−0.154	0.969
GEOG*GEN.LANG	−0.121	0.865
LANG*GEN.GEOG	−0.241	0.991

Africa than do the other Balearic islands. Therefore our results appear to confirm the historically derived hypothesis of a Carthaginian origin of Ibiza. In this case the gene pool of the population is a reflection of its unique history.

The genetic differentiation of Ibiza from the other two Balearic islands could have been influenced by a founder effect and other stochastic processes. The plot between mean per locus heterozygosity and r_{ii} reveals that, although Ibiza has levels of heterozygosity similar to those of Minorca and Majorca, the distance from the centroid of distribution is greater. This study demonstrates that unique historical events combined with the action of stochastic processes can explain much of the observed genetic variation in island populations. However, the action of natural selection cannot be ignored in Ibiza because of the high incidence of malaria and the observed statistically significant deviation of the Duffy system from expectation.

The significant pairwise correlations between linguistic distances with geographic and genetic distances—with no apparent association demonstrated with partial and multiple correlations—suggest the effects of much historical "noise" on Mediterranean populations. For example, the migration of Catalans to the Balearic Islands followed by the acquisition of the Spanish language by the original inhabitants of Ibiza complicates the simple associations that one would expect to find in island populations. The effects of stochastic processes are also compromised by the high level of gene flow.

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