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Are the Basques a Single and a Unique Population?

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Summary

Different analyses of genetic polymorphisms performed on the Basque population have suggested a possible heterogeneity of the Basques and a singularity of their genetic characteristics. In this paper, both aspects are analyzed by means of the genetic study of seven polymorphic systems—ACP, ADA, AK, ESD, PGD, GC, and HP—in 854 autochthonous individuals from the province of Vizcaya. The individuals were classified as being from the regions of Arratia, Guernica, Durango, Uribe, Marquina, Lea, and Bilbao, on the basis of the birthplaces of their four grandparents. Analyses for heterogeneity of the gene frequencies distribution suggest that there is a moderate genetic heterogeneity, probably produced by centuries of geographical and administrative isolation of these regions. The comparison with caucasoid populations, performed using the principal components analysis and Cavalli-Sforza and Edwards arc distance, indicates that the subpopulations of the province of Vizcaya have experienced little genetic exchange with other caucasoids and that the distribution of their genetic frequencies differentiates them from other populations.

Introduction

The Basque population is located in seven provinces on both sides of the Pyrenees; four of these provinces (Vizcaya, Alava, Guipuzcoa, and Navarre) belong to Spain, and the remaining three (Labourd, Basse-Navarre, and Soule) belong to France. All seven share the same ethnic origin, the same culture, and the same language (Basque or Euskera).

The Basque language is one of the few pre-Indo-European languages of Europe, and it has been described as an ancestral language with no living relatives. This and other historic data show that the Basque people have remained in their present location for a very long time, avoiding the eastern European invasions of the Iron Age and having very little contacts with the Celts and the Iberians.

Blood group analysis has shown the Basques to have their own genetic characteristics (Mourant 1983), such as the highest frequency in Europe of allele "d" of Rh and the lowest frequency in Europe of allele "B" of the ABO system. The analysis of erythrocytic enzymes and plasma proteins indicates that in these systems the Basques are also different from geographically neighboring populations (Aguirre et al. 1989).

Elsewhere (Aguirre et al. 1989), we compared our results on the Basque population with data from other reports on Basques and proposed that a certain degree of genetic heterogeneity could exist within the Basque population. If there is genetic heterogeneity, then there must be more or less isolated subpopulations with different genetic characteristics. To explore the existence of subpopulations, we began our study in the province of Vizcaya. Apart from being geographically structured in the form of valleys, this province has traditionally been divided into areas which can be compared with valleys and river basins.

There are historical, social, and linguistic features of Vizcaya which seem to indicate that for centuries there has been some isolation of areas. This might be conducive to the creation of genetically differentiated subpopulations: the ancient legislative organization of this province was based on the valleys: the hamlets, farmhouses, and land of a valley were grouped in "merindades," where affairs affecting the community

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were settled. For affairs affecting the province, the representatives of the merindades met in what were known as general assemblies. There is no record of the origins of these legislative bodies, since written records were not kept until 1342. They are, however, thought to be very ancient. On the other hand, there have always been two clearly differentiated social types: one on the coast, working on fishing (at least since the 11th century), and the other, larger group inland, with a life-style and customs revolving around farming and cattle raising. These groups have traditionally been differentiated, even at their geographical limits. The fact that various dialects and variations in the Basque language can be detected is another point in support of the theory that some degree of isolation existed among the Basques. Thus, in Vizcaya various maps have been proposed to show the limits of the varieties of Vizcayan dialect (Bonaparte 1858, 1863, 1869). These coincide broadly with the geographical, legislative, and social structure.

In the present study we shall attempt to prove whether there exists genetic heterogeneity in Basques, by analyzing seven polymorphic systems in the natural subpopulations of one of the Basque provinces: Vizcaya. We shall further attempt to discover whether these populations show any peculiar genetic characteristics and to contribute to a greater knowledge of the genetic relationship of the Basques to other caucasoid populations.

Material and Methods

Although there is no census of the present autochthonous Basque population, we can state that it is not very large, owing to constant mixing, since early this century, with immigrant populations from the rest of the Iberian Peninsula. In spite of its low numbers, it is not difficult to pick out the Basques from the individuals belonging to other populations which cohabit with them, as their surnames are clearly differentiated. In the present study we analyzed blood specimens from 908 autochthonous individuals whose eight immediate forbears had Basque surnames and all four of whose grandparents were natives of Vizcaya. Once those who were related in the first or second degree were eliminated from the sampling, we were left with 854 individuals.

Samples were taken from the following subpopulations or natural areas of Vizcaya: Uribe, Guernica, Lea, Marquina, Durango, Arratia, and Bilbao (fig. 1). We used geographical, social, and linguistic data to establish the limits of each area.

Each individual sampled was classified as belonging to one of the above areas, on the basis of the birthplaces of his four grandparents. Therefore, if his four grandparents were all from the same area, the individual was put into the subpopulation, and if they came from more than one area the individual was classified as "mixed" (e.g., maternal grandparents from Guernica and paternal grandparents from Durango). This classification system ensures a representative sample of ancient subpopulations that may not necessarily be in accordance with modern biological populations.

Ten milliliters of blood with ACD anticoagulant were taken from each donor. Each sample was separated into fractions, washed, and hemolyzed according to conventional techniques (Aguirre et al. 1989). Samples were kept at $-80°C$ until subsequently analyzed.

In order to characterize the samples genetically, various red cell isozyme types were analyzed: for acid phosphatase (ACP), Karp and Sutton's (1967) run conditions and Harris and Hopkinson's (1976) A&B stain technique, as described by M. de Pancorbo et al. (1986), were used; for adenosine deaminase (ADA), adenylate kinase (AK), and phosphogluconate dehydrogenase (PGD), Harris and Hopkinson's (1976) techniques were used. The types for esterase D (EsD) were obtained by Harris and Hopkinson's (1976) methodology, in which 4-methyl-umbellyferil acetate was used as substratum and in which 2-mercaptoethanol (0.2%) was added to starch gel.The plasma protein haptoglobin (Hp) and Gc system (Gc) phenotypes were obtained using the Smithies' (1959) buffers method and Giblett's (1969) stain and Constans and Cleve's (1979) procedure, respectively.

Calculation of expected frequencies in the equilibrium was done by the usual method (Li 1968), except in small samples, where Levene's (1949) correction was applied. For the F_{ST} statistic (Wright 1965, 1978), the basic formula used was $(1 - F_{IT}) = (1 - F_{IS})(1 - F_{ST})$, where F_{IT} and F_{IS} are the fixation indexes of individuals, relative to the total population and its subpopulations, respectively.

The significance of the F_{ST} values, for a k-allelic locus, was determined by Workman and Niswander's (1970) method: $X^2_G = 2N_T(k-1)F_{ST}$, where N_T is the number of individuals and $(k-1)(j-1)$ is the df to be considered for j subpopulations. According to these authors, a single estimate for genetic heterogeneity in a population is given by $\Sigma\chi^2_G$, where the summation is over all independent loci.

The analysis of heterogeneity among populations was also estimated as χ^2_{HET}, on the basis of the gene-

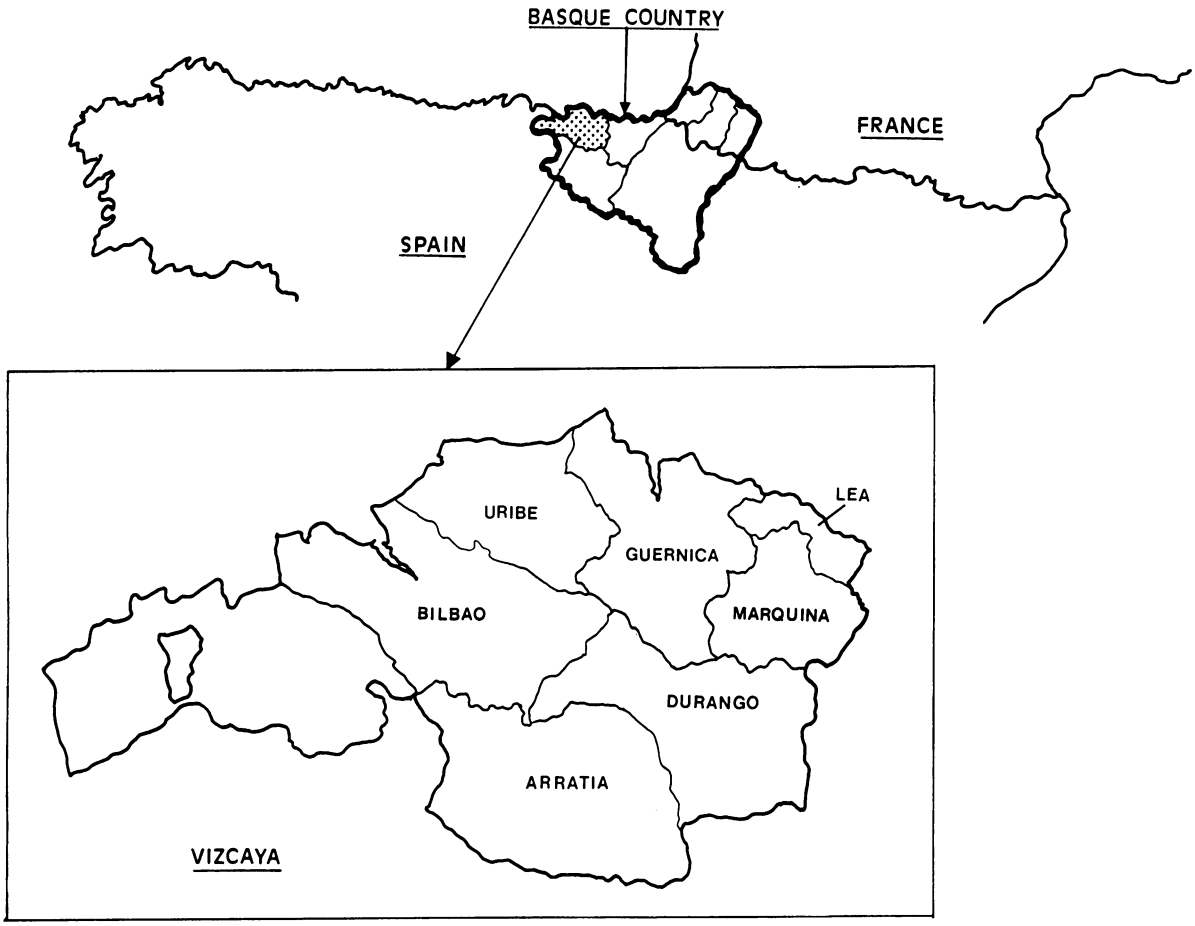

Figure 1 Geographical distribution of Vizcayan regions

frequency contingency tables, with $(m-1)(n-1)$ df, where m is the number of populations and n the number of alleles. The total χ^2 was the sum of the $\chi^2_{\text{HET's}}$ over all loci.

To learn what genetic relationship exists between the Basques and other caucasoid populations, we carried out a principal components analysis by means of the SPAD program (Lebart et al. 1977) and using Cavalli-Sforza and Edwards (1967) arc distance, using the Biosys-1 program (Swofford and Selander 1989). Principal components analysis is a special case in multivariant factor analysis. Its aim is to simplify the structure of the data so as to enable one to explain, in a few components, as much as possible of the information contained in the original variables. The analysis attempts to select one principal component (F_1) which explains most of the variance of the variables used in the analysis. Once that component is found, it is subtracted from the variables, and from the remaining variance the second principal component (F_2), is selected, orthogonal to the first, and so on until the n components are obtained. The principal components are defined as Y variables, a linear combination of the observable variables, with the property of having maximum variance; they are obtained by diagonalizing the covariance matrix (Cuadras 1981). For a detailed description of the mathematical methodology, see the report by Lebart et al. (1977).

Results

For each system and for each area the distribution of phenotypes and the gene frequencies are given in tables 1 and 2, respectively. When possible, the χ^2 values for deviation from equilibrium for all areas and systems were computed (table 2, last column). Only

Table 1

Phenotype Distribution in Basque Populations Analyzed

	Uribe	Guernica	Marquina	Lea	Arratia	Durango	Bilbao	Mixed
ACP:								
AA	17	4	3	4	2	8	2	30
AB	56	42	28	27	24	27	7	113
BB	67	51	39	34	35	36	18	159
AC	1							1
BC					2	3		4
Total	141	97	73	65	63	74	27	307
ADA:								
1-1	134	91	71	65	62	70	26	290
2-1	6	5	1		1	4		15
2-2								1
Total	140	96	72	65	63	74	26	306
AK:								
1-1	135	86	64	60	51	70	24	278
2-1	7	11	8	5	11	4	3	28
2-2					1			1
Total	142	97	72	65	63	74	27	307
EsD:								
1-1	122	86	58	51	55	66	22	269
2-1	16	9	14	14	7	8	3	35
2-2								3
Total	138	95	72	65	62	74	25	307
PGD:								
AA	136	94	71	64	63	74	27	302
AC	4	3	1	1				6
Total	140	97	72	65	63	74	27	308
GC:								
1-1	63	38	20	33	27	35	10	149
2-1	65	42	43	25	33	39	15	132
2-2	15	17	12	7	4	3	2	25
Total	143	97	75	65	64	77	27	306
HP:								
1-1	28	14	18	5	9	11	4	55
2-1	70	46	32	37	30	41	19	163
2-2	44	36	22	23	24	23	4	91
Total	142	96	72	65	63	75	27	309

two values significant at the 5% level appeared: that for the Gc system in Durango, which showed a slight excess of heterozygotes, and that for the Hp system in Bilbao, which could be the result of a sample-size error.

The ACP system in the populations of Vizcaya shows the presence of two common alleles (ACP^a and ACP^b) and one rare one (ACP^c). The ACP^a allele frequencies are among the lowest values found among European populations, while the ACP^b allele frequency is one of the highest. The ACP^c gene is absent, or it occurs with very low frequency. These extreme frequencies situate this population at one end of the cline described for the Iberian Peninsula (M. de Pancorbo et al. 1986) and are the reason why, for this systems, the population of Vizcaya shows significant differences from practically all the other European populations analyzed—such as Germany, Switzerland, Norway, Sweden, Italy, England, Ireland, Iceland, Bulgaria (cited by Becker 1980), Poland (Wolanski et al. 1983), France (Vergnes et al. 1980*a*) and others—and even from other Spanish populations such as Galicia (Carracedo and Concheiro 1982), Barcelona (Moreno and Moral 1981), Menorca (Moral 1986), Meseta Central (Goedde et al. 1972), etc.

Similar points are found for the ADA system. The frequency of gene ADA^2 is very low (0.7%–2.8%) or absent among Vizcaya's subpopulations. Except for

Table 2

Gene Frequencies, X^2 Test, Hardy-Weinberg Equilibrium, and X^2_{HET}

	Uribe	Guernica	Marquina	Lea	Arratia	Durango	Bilbao	Mixed	X^2_{HET}
ACP^a	.323	.258	.233	.269	.222	.291	.204	.283	
ACP^b	.674	.742	.747	.731	.762	.689	.796	.709	
ACP^c	.004	. . .	.021	. . .	.016	.020	. . .	.008	
X^2	3.14 (1 df)	1.68 (1 df)	1.46 (1 df)	.20 (1 df)	1.29 (1 df)	2.16 (1 df)	1.09 (1 df)	2.46 (2 df)	7.36 (6 df)
ADA^1	.979	.974	.993	1.000	.992	.973	1.000	.972	
ADA^2	.021	.026	.007	. . .	.008	.027	. . .	.028	
X^2	.06 (1 df)	.06 (1 df)	.00 (1 df)	. . .	.00 (1 df)	.04 (1 df)	. . .	2.86 (1 df)	7.19 (6 df)
AK^1	.975	.943	.944	.962	.897	.973	.944	.951	
AK^2	.025	.057	.056	.038	.103	.027	.056	.049	
X^2	.08 (1 df)	.32 (1 df)	.22 (1 df)	.08 (1 df)	.28 (1 df)	.04 (1 df)	.06 (1 df)	.13 (1 df)	14.24 (6 df)*
EsD^1	.942	.953	.903	.892	.944	.946	.940	.933	
EsD^2	.058	.047	.097	.108	.056	.054	.060	.067	
X^2	.49 (1 df)	.21 (1 df)	.77 (1 df)	.87 (1 df)	.19 (1 df)	.21 (1 df)	.07 (1 df)	2.36 (1 df)	7.75 (6 df)
PGD^a	.986	.985	.993	.992	1.000	1.000	1.000	.990	
PGD^c	.014	.015	.007	.008	. . .	. . .	. . .	.010	
X^2	.02 (1 df)	.02 (1 df)	.00 (1 df)	.00 (1 df)	. . .	. . .	. . .	.03 (1 df)	5.17 (6 df)
GC^1	.668	.608	.553	.700	.680	.708	.648	.703	
GC^2	.323	.392	.447	.300	.320	.292	.352	.297	
X^2	.09 (1 df)	.81 (1 df)	1.92 (1 df)	.46 (1 df)	2.17 (1 df)	3.88 (1 df)*	1.28 (1 df)	.29 (1 df)	12.25 (6 df)
HP^1	.444	.385	.472	.362	.381	.420	.500	.442	
HP^2	.556	.615	.528	.638	.619	.580	.500	.558	
X^2	.00 (1 df)	.01 (1 df)	.85 (1 df)	3.53 (1 df)	.01 (1 df)	1.12 (1 df)	4.48 (1 df)*	1.49 (1 df)	7.24 (6 df)

NOTE.—Mixed have not been included in the X^2_{HET} analysis.
* $P < 0.05$.

Ouzom (Vergnes et al. 1980*a*), these values are the lowest reported for a European population. Comparisons with other European populations such as Denmark, Germany, France, Poland, Portugal, Italy, Ireland, Finland, Great Britain (all cited by Weissman et al. 1982), Greece (Detter et al. 1970), with Pyrenean populations (Vergnes et al. 1980*a*) or with Spanish populations such as Menorca (Moral 1986), Gerona and Barcelona (Moral and Panadero 1984), Galicia and Andalucia (Goedde et al. 1972), etc. showed significantly different results.

In the AK system, the frequency of allele AK^2 in Vizcaya varies from 2.5% in Uribe to 5.7% in Guernica, with the exception of Arratia, whose AK^2 frequency of 10.3% is one of the highest in Europe, surpassed only by that of the population of Ireland (Palsson et al. 1970). It is even higher than that in populations known to have high frequencies of this allele, such as the Plati (Tills et al. 1983), the Parsis (Undevia et al. 1972), and the Maharatas and Gujaratis Indians (Blake et al. 1970). For this enzyme system, those named above are the only caucasoid populations analyzed in which comparison with Arratia does not show significantly different results. The remaining areas of Vizcaya show frequencies similar to most other European frequencies, and only populations with very low allele AK^2 values, such as Sardinia (Floris et al. 1985), Galicia (Goedde et al. 1972) or Capcyr and Baronnies (Vergnes et al. 1980*a*), show significant differences.

The frequency of allele EsD^2 in Vizcaya varies from 4.7% in Guernica to 10.8% in Lea. This frequency is similar to that of allele EsD^2 in other European populations, and it only differs significantly from a few populations with even lower frequencies for this allele, such as Galicia (Carracedo and Concheiro 1983), Teide in the Canaries (Martell et al. 1986), or Pallars Sobirá in Lérida (Moral et al. 1986), all of which are in Spain. However, most of the areas of Vizcaya show EsD^2 frequencies significantly lower than those in other European populations, such as Portugal (Amorim and Siebert 1982), Italy (Gruppioni

and Pettener 1982–83), France and Switzerland (Vergnes et al. 1980*b*), Denmark (Dissing and Eriksen 1984), Poland (Dobosz 1983), Germany (Blake 1976), Great Britain (Mitchell et al. 1982), Belgium (Brocteur et al. 1980), the Plati (Tills et al. 1983), etc.

In Vizcaya the PGD system shows one allele (PGD^a) of very high frequency, between 98.5% and 100%, and another (PGD^c) that either is of much lower frequency or, in some areas, is absent. Although PGD^c frequency is low, similar values have been found in various European populations, such as Ireland (Tills et al. 1971), Bareges, Ouzom, and Capcyr in France (Vergnes et al. 1980*a*), Italy (Gruppioni and Pettener 1982–83), etc. However, the areas of Vizcaya differ from most central and northern European populations, which are characterized by higher frequencies of this allele.

In the Gc system, we detected two alleles, which show a wide range of variation in the areas of Vizcaya. Allele Gc^1 has frequencies varying from 55.3% to 70.8%, and allele Gc^2, which is less frequent in all cases, varies from 29.2% to 44.7%. It may be observed that two areas, Guernica and Marquina, have higher frequencies for allele Gc^2. These areas, together with both another Basque population studied by Constans (1975) and others French Pyrenees populations such as Bareges and Capcyr (Constans 1975), represent the significantly highest frequencies of allele Gc^2 in Europeans. The remaining areas of Vizcaya have Gc^2 frequencies of between 30% and 35%, and are not differentiated from most other European populations.

Allele Hp^1 is the less frequent of the two detected in haptoglobin protein in Vizcaya, except in Bilbao, where alleles Hp^1 and Hp^2 have the same frequency. If we exclude this case, because of the small size of the sample, Hp^1 allele frequency varies from 36% to 44%. These frequencies are within the range of variation found for most of the European populations described, so no singular values of Hp are observed in Vizcaya.

In view of the differences we found in gene frequencies between the different areas, we examined the extent of heterogeneity with the help of a contingency χ^2 for independence and Wright's F statistics. The χ^2 values for independence among areas (χ^2_{HET}) are significant in one of the seven polymorphic systems studied: AK (see table 2). Furthermore, the total χ^2 pooled over all loci is significant ($\chi^2 = 61.20$; 42 df; $p < .05$). Wright's F statistics, and principally the F_{ST} statistic, are often used to estimate interpopulation genetic diversity. Values are obtained on the basis of statistics F_{IT} and F_{IS}. Most of the genetic systems studied showed slightly negative F_{IS} and F_{IT} values, with the mean F_{IT} and F_{IS} also being negative (Table 3). If the areas of Vizcaya are considered as subpopulations, we again obtain significant values for the AK system, and a significant mean F_{ST} value.

Once the characteristics of the areas of Vizcaya were known for each polymorphic system, we performed a principal component analysis using the set of systems presented in the present paper, in other to discover the genetic relationships established between present-day Basques and other caucasoid populations. We included all allele frequencies for the areas of Vizcaya and other caucasoid populations on which we were able to obtain information for the seven systems.

After the principal component analysis, we obtained eight eigenvalues. From component 3 onward, the eigenvalues obtained were very similar to each

Table 3

F_{IS}, F_{IT}, and F_{ST} Values

Systems	F_{IS}	F_{IT}	F_{ST}	X^2_{FST}	df
ACP	−.005	.003	.008	17.33	12
ADA	−.023	−.013	.009	9.65	6
AK	−.021	−.008	.012	12.96*	6
EsD	−.082	−.074	.007	7.43	6
PGD	−.013	−.006	.006	6.46	6
Gc	−.090	−.078	.011	12.06	6
HP	−.096	−.086	.009	9.72	6
Average value	−.064	−.054	.009	75.602**	48

NOTE.—Mixed have not been included in the X^2_{FST} analysis.

* $P < .05$.

** $P < .01$.

other, and the variability explained by each of them was greatly reduced. When both characteristics occur simultaneously, it is deduced that there are no main axes, since there is no direction of maximum variability (Anderson 1963). Therefore, we performed a hierarchical classification analysis using the reciprocal neighbor method, with only the information from the first three factors, which reflect 77% of the total variance in allele distribution (see cluster in fig. 2). According to this cluster, the populations of Vizcaya are grouped together and clearly differentiated from the group of European caucasoid populations and from extra-European caucasoids.

Very similar results are obtained using the Cavalli-Sforza and Edwards arc distance after cluster analysis using the unweighted pair group method (UPGM) (fig. 3). In this cluster, too, two clearly differentiated groups may be appreciated: on the one hand, the Basques; on the other, the other caucasoids, which are in their turn divided into two subclasses, one for Europeans and the other for non-Europeans.

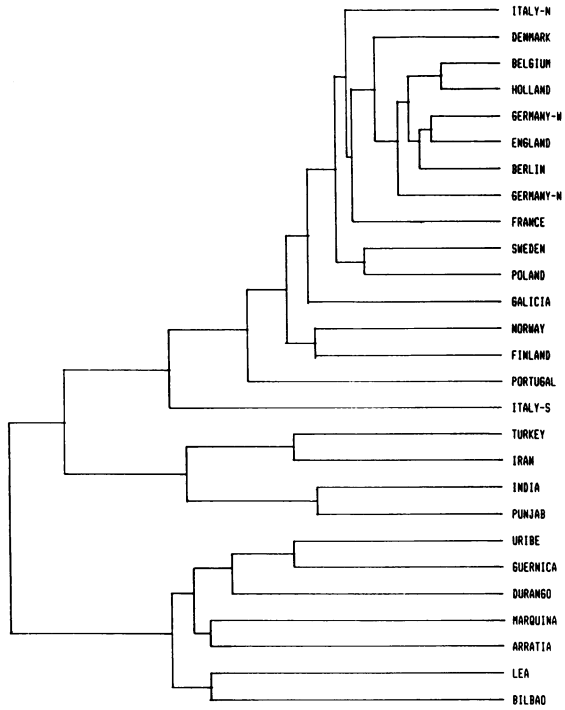

Figure 3 Cluster UPGM of caucasoid populations from Cavalli-Sforza and Edwards arc-distance matrix.

Discussion

The Basques have always occupied, and indeed still do, a land characterized by its complex geographical structure, with many fluvial and orographic accidents occurring in the region. Probably influenced by the geographical substratum, the Basque population has, over the centuries, developed a social organization based on natural units: valleys or areas. These natural units, having a considerable degree of autonomy in administrative matters, are likely to have acquired some degree of genetic isolation.

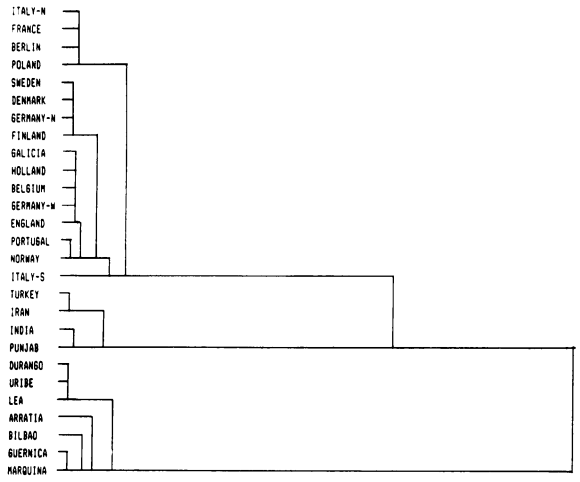

Figure 2 Hierarchical classification of caucasoid populations according to results of principal component analysis.

The null hypothesis of homogeneity among areas is only statistically rejected for one locus, though the failure to reject this null hypothesis for the other six loci is not proof of homogeneity for these systems. Furthermore, the analysis of the heterogeneity, for all loci, among the areas of Vizcaya, seems to point to the existence of a moderate interpopulation differentiation which seems due to the effect of random genetic drift moderated by a small amount of migration but which does not affect all the systems equally. In those systems where significant differences in gene frequency distribution are observed, there are one or two areas distanced from the rest. But these are not the same areas in different genetic systems (Arratia in AK, Lea in EsD, and Marquina in Gc).

There is no apparent historical, geographical, or linguistic reason to think that these areas may have characteristics which could differentiate them from the rest. Neither is there any reasons to suspect that there are differences among loci in interarea heterogeneity. The Lewontin and Krakauer method (1973) for de-

tecting natural selection by using the F_{ST} values is not significant in the seven loci; i.e., the observed distribution does not differ significantly from that expected theoretically under neutral conditions. Future analysis in these areas of Vizcaya, using new genetic systems, may clarify this situation and detect heterogeneity which may affect areas which in the present paper showed no differences.

On the other hand, even today we know little of the origin of the Basques. It has been suggested that many of the mesolithic settlers of western Europe could have mixed with newcomers from the neolithic to give rise to present-day Europeans but that a few groups of mesolithic men in the Pyrenean region could have remained sheltered from subsequent invasions (Cavalli-Sforza 1988), thus giving rise to present-day Basques (Mourant 1983). It has also been stated that the Basques are a people who have successfully resisted absorption by a succession of conquering or neighboring cultures (Collins 1986). If this is so, present-day Basques can be considered as a relic of the first populators of Europe (Piazza et al. 1988).

This idea agrees with the results of the principal component analysis comparisons and the cluster from Cavalli-Sforza and Edwards arc-distance matrix, for comparisons of the Vizcayan populations with other European populations of the seven polymorphic systems. Though part of the differences found among Basques may be originated by the sampling methods (the Basque subdivisions are more internally differentiated than very geographically distant countries in Europe), both cluster analyses indicate that the subpopulations of Vizcaya are more different from remaining caucasoid populations than from each other, since they form a close-knit group which is clearly differentiated from both the European and non-European groups. Although this result may not be considered as definitive support for the hypothesis of a different origin for Basques than for other present caucasoid populations, it does at least demonstrate that the Basques have had little genetic exchange with related populations and that even today they maintain a genetic make-up which is clearly differentiated from that of other similar populations.

Acknowledgments

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