

Review Synthetic Article

Sardinian Population (Italy): a Genetic Review

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Abstract - For years the population of Sardinia has been object of numerous studies in the fields of anthropology and population genetics. Researches on genetic structure of Sardinian population, performed with of both classical and DNA markers, revealed an extremely complex picture of the relationships between Sardinian and other Italian and Mediterranean populations, that can be explained by Sardinian's historical and demographic past. A high degree of internal heterogeneity was also found and it can be attributed first to strict isolation and consequent high levels of endogamy and consanguinity, secondly, to selective factor linked to endemic malaria that influenced the distribution of some gene frequencies. Finally an influence on Sardinian's biological history could be attributed to the demographic events such as low population density and scant matrimonial movement, which triggered off phenomena of genetic drift.

Key Words: *genetic markers, genetic structure, Sardinia.*

Introduction

Sardinia, an autonomous region of insular Italy, covers an area of 24,000 square km and it is divided into eight provinces. The capital of the region is the city of Cagliari. The geological history of Sardinia dates back at least to the beginning of the lower Cambrian period. Flint-stone instruments made according to the “Levallois” and “Clactonian” techniques attest to the presence of humans in Sardinia from the lower Palaeolithic period, but no human remains were found along with these instruments.

The most ancient recent remains dates back about 14,000 years ago (upper Palaeolithic) and were found in the Corbeddu cave at Oliena. During the Neolithic period two main cultures are present: the culture of megalithic circles, either of “Arzachena” or “Gallurese”, limited to the northern region. The most evident aspects of this culture are the burial monuments formed by circles of thickly embedded stones around a quadrangular box. Material aspects place this culture within the phenomenon of commercial and cultural trading, which took place along the east-west route of the Mediterranean Sea between the end of the 4th millennium and the 3rd millennium B.C. The culture of S. Michele or Ozieri, originating from outside the island, adapted itself by absorbing regional elements (Lilliu, 1988). One of the characteristic features of this culture consists of the small caves excavated in rock for the purpose of collective burials (named *Domu de Janas*). The underground vaults and their symbology, the pillars, the statuettes and the pottery suggest active exchange with middle-eastern parts of the Mediterranean, most particularly the Aegean area and the Cyclades.

The Bronze Age signals the beginning of a new path of the Proto-Sardinian civilization, marked by its typical monument: the Nuraghe. The similarities in the architectural structure between Nuraghe, taloiois and “towers” indicate exchanges between Sardinia, Balearic Island and Corsica. Another interesting phenomenon is the expansion of metalworking. Bronze objects are comparable to those of France and Iberian Peninsula (Lilliu, 1988). The Sardinian language, classified among neo-Latin languages, has few main subdivisions and many variants. For instance, Blasco Ferrer (1984) suggests that Sardinian is divided into four diasystems: those of Sassari, Gallura, Logudoro and Campidano. The two latter diasystems show three and eight variants

respectively. Contini (1979), on the other hand, proposed ten main variants and as many as 30 subdivisions. Thus, even from a linguistic point of view, Sardinia appears to be extremely subdivided. The greatest constant in the history of Sardinia is the persistent shortage of humans (Day, 1988).

The demographic history of Sardinia is that of a population which over the centuries has battled against extinction. It is believed that from prehistory to 1700 A.D., the Sardinian population never exceeded 300,000 inhabitants and a population density was about six inhabitants per square km. Despite the numerous successive colonisations the island has never benefited from real colonization in terms of demographic development, urban growth and rural settlement. Around 1348 A.D. the Black Plague reduced the population by half. The number of inhabitants of the seven main cities fell by more than 75%, from about 50,000 to 12,000. The years between the plague of 1348 and the Sardinian parliament of 1485 proved the worst ever for the Sardinian population on account of wars, six subsequent epidemics of plague, famine, food shortages and the deportation of rebels against the Spanish crown. Between the census of 1485 and that of 1589 there is an increase of 40,000 families, or roughly 160,000 inhabitants. However in 1591-92, a terrible famine marked the beginning of another period of meteorological and epidemic misfortunes.

The census carried out by the Savoy in 1728 shows that the population, which numbered about 310,000, had overcome the effects of these great calamities. From this period to the present day, a positive trend of demographic development has characterized the Sardinian population. Nowadays the density has risen to around 70 inhabitants per square km compared with a national average of 187. The Sardinian population was the object of deep studies by geneticists and anthropologists and in this paper we review the most important results published until now.

Classical Genetic Markers

Data on classical genetic markers show an extremely complex picture of relationship between Sardinia and other Italian and Mediterranean populations and a high level of internal heterogeneity. Sardinians are characterized by extremely high frequencies of two mutant genes: the gene of thalassemia and the gene causing the lack

of glucose-6-phosphate dehydrogenase enzyme (G-6-PD). The gene of thalassemia has an average value of about 20%, reaching a maximum value of 36%. The Mediterranean variant of G-6-PD has an average frequency of about 26%, with a maximum of 35%.

The distribution of the two alleles is not uniform throughout the island and a negative and highly significant correlation with altitude was found (Siniscalco et al., 1966; Vona and Porcella, 1984). The villages mainly affected by the presence of the two mutants are those of the plains and the coastal hills. The mountainous regions have lower frequencies of the two alleles. This correlation is supported by the trend of the two genes in the populations distributed along an axis running from the gulf of Oristano, in the west of the island, across the central mountainous area, to the eastern coastal side. The frequencies are very high in the two coastal sides and decrease sharply towards the central mountainous area (Bodmer and Cavalli Sforza, 1977).

The dimension of genetic variability within the island Sardinia was analysed through 12 classical genetic markers on the basis of its 21 linguistic domains (Cappello et al., 1996), according to the classification suggested by Contini (1979). The genetic tree performed by genetic distances had a star-like structure that underlines a large genetic variance in each linguistic domain, confirming the heterogeneity of the island (Figure 1). Only two clusters of highly related populations seem to have been separated and to have maintained a genetic identity through their evolution: the cluster constituted by the domains of Nuoro and Orosei– Siniscola associated with the highest bootstrap value (85%), and the cluster constituted by domains of Campidano of Oristano, Campidano of Cagliari, Trexenta Parteolla and Sulcis – Iglesiente, with a bootstrap percentage of 56%. The genetic structure of Sardinia seems mainly rooted in two areas: Nuorese, included in the archaic zone, and the south-western area (Campidanese). The main findings of the work by Cappello et al. (1996) are summarized as follows: 1) the microgeographic heterogeneity of gene frequencies in Sardinia is correlated with archaeological, linguistic and historical evidence; 2) the gene distribution is statistically significant correlated with the distribution of linguistic variants.

A study based on the frequencies of several classical genetic markers shows some of the distinctive features that set Sardinians apart from other Mediterranean populations: very high frequencies of RH*Cde, MN*M, PGM1*1 and a very low value

of RH*cde (Moral et al., 1994). The genetic distances of Reynolds (Reynolds et al., 1983) were used, through Delauney's triangulation and the Monmonier algorithm (Monmonier, 1973), to identify the presence of genetic boundaries within the Mediterranean basin. In the Delaunay's triangulation the sample points, which represent the localities of the studied populations, are connected by lines to form triangles.

By using the triangles, each piece of the surface will be continuous. Each edge is also associated with a genetic distance value. A perpendicular line across the edge showing the highest genetic distance, which is the origin of the first boundary, is traced to identify the zones of genetic boundary. The first boundary is then extended across the adjacent edge showing the highest distance and so on, until it reaches the limit of the network (Monmonier, 1973); Sardinia and Corsica appear clearly isolated in this context by a strong genetic boundary (Vona et al., 2002) (Figure 2). According to Piazza et al. (1988) Sardinia results an outlier in Europe because many genes show a significant deviation from regional average gene frequencies. These peculiar frequencies cause a substantial diversification between Sardinians and northern African, European and Mediterranean populations.

Figure 1

Neighbor- Joining tree of the Sardinian population from the linguistic domains

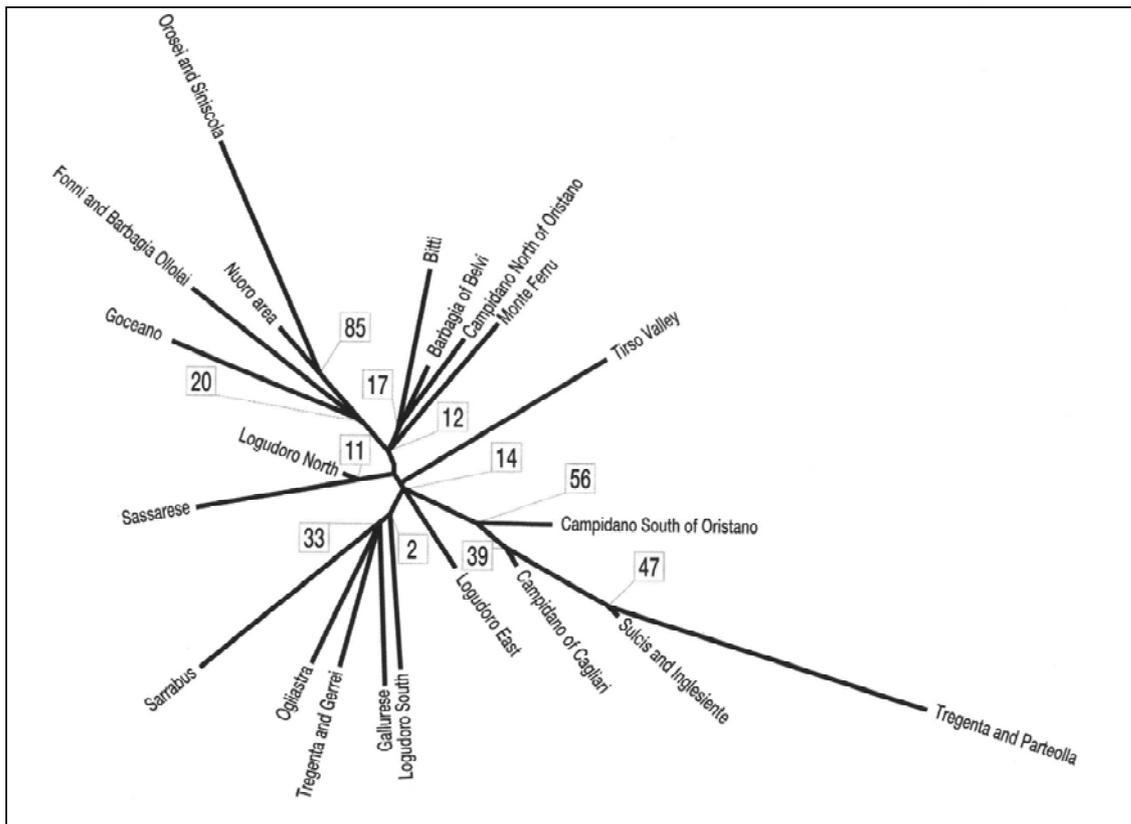
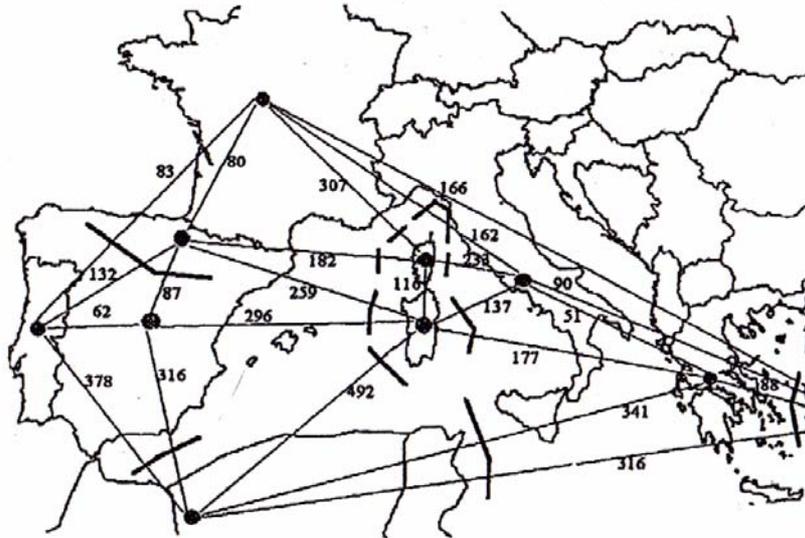


Figure 2.

Genetic boundaries in Mediterranean emerged applying Dalunej's triangulations.



HLA

The study of the HLA (Human Leukocyte Antigens) system confirms the peculiarity of Sardinians among Mediterranean populations (Contu et al., 1992; Vona et al., 1997; Lampis et al., 2000; Grimaldi et al., 2001), and it suggests an internal homogeneity (Contu et al., 1992; Lampis et al., 2000). But there are some particular observations that do not fit with the uniform distribution of alleles and haplotypes of the HLA system. For example, allele B*35 shows a different distribution within Sardinia (Contu et al., 1992); frequencies of haplotype A2-Cw7 and B35-Cw7 have distributions significantly different in the population of Sassari and Nuoro (Vona et al., 1997) when they are compared with other areas of Sardinia studied by Contu et al. (1992).

The study of HLA suggests important contacts between Sardinia and northern Africa highlighted by high frequency of haplotype A*33-Cw*08-B*14. Also haplotype A*30-Cw*0501-B*18, which has a high frequency in Sardinia (12.5%) has an African origin, from which it expanded towards the Middle East (Grimaldi et al., 2001).

Molecular Markers

Autosomal molecular data show Sardinians as the most differentiated population in the Mediterranean basin and Europe. The genetic peculiarity of Sardinians was interpreted as the result of genetic drift and geographic isolation, with a limited genetic impact from conquests of the islands during history (Moral et al., 1994; Calò et al., 2001).

Several works also underlined an obvious heterogeneity within Sardinia itself (Calò et al., 1998; 2000). Through the analysis of some minisatellites, the population from Campidano of Cagliari (southern Sardinia) clustered, albeit in a distinct position, with other Mediterranean and European populations. On the contrary, the population of Nuoro appears highly differentiated in comparison both with other Sardinians and with all the other Euro-Mediterranean populations. A research based on the analysis of 11 Alu insertions (Calò et al., 2005) confirmed the high degree of isolation for Nuorese.

The molecular analysis shows that the most frequent mutation among the thalassemia carriers is the 39 codon nonsense (95.7%). Two other common mutations are the frameshifts at codon 6 and 76, with frequencies of 2.1% and 0.7% respectively, which conversely are relatively rare in other Mediterranean populations (Rosatelli et al., 1992). The high frequency of $\beta^{\circ}39$ mutation differentiates Sardinians both from eastern Mediterranean populations, characterized by the prevalence of β^+ IVS1-110 mutation, and from populations from other Western Mediterranean countries, which show more kinds of mutations, including $\beta^{\circ}39$, but with much lower frequencies. Such differentiation is found also when beta-globin cluster haplotype frequencies are analysed both in a general population and in $\beta^{\circ}39$ carriers (Latini et al., 2003; Piras et al., 2005). Haplotype frequencies confirm the lack of genetic homogeneity in the island. In fact, when a genetic tree is drawn with populations from other continents, Sardinian samples are located in different branches of the tree. Moreover, the cited authors report

the presence in some Sardinian areas of the typical African haplotype 5, identified with both 5 and 7 restriction enzymes (-+--+ and -+--+-, respectively) (Latini et al., 2003; Piras et al., 2005). Haplotype 5 is absent among both normal and thalassemic samples from Mediterranean populations (Flint et al., 1992). The presence of this haplotype was explained by the authors as a recent acquisition by the Sardinian population and it is very likely that it was introduced into the island by African slaves during the Carthaginian and Roman dominations.

MtDNA

The analysis of mtDNA with restriction enzymes shows that Sardinians have the same haplogroups as European populations. However, some frequencies such as haplogroups U, V, X reach about 12% in the whole Sardinia, whereas in Europe their frequency exceeds 22%. Besides, the frequency of haplotype J in Sardinia (5.5%) is approximately half the European frequency (10.8%). According to Barbujani et al. (1995), the enzymatic study of mtDNA shows that Sardinians could constitute a stable population in contrast with continental populations, characterized by two demographic expansions: after the last maximum glacial period (20,000 – 16,000 BP), and at the beginning of the Neolithic period. The Sardinian population had a slower growth and an independent evolutionary history, due to its isolation. The same authors underline the presence of a certain internal variability shown by the two morphs, present in all the comparison populations. However the frequencies differ across the island, with the limits of the range recorded by two villages of the same central area: morph 1 between 0.558 of Desulo and 0.926 of Orosei; morph 8 between 0.028 of Orosei and 0.306 of Desulo.

When some areas of the island are analysed on the basis of haplotype frequencies, an internal differentiation is obvious. Haplotype H varies from 41.2% at Gallura (northern area) to 75% at Ogliastra (central-eastern area). The two populations also signal the extreme values for the frequencies of haplotypes U, V and X, which vary from 27.5% in Gallura to 10% in Ogliastra (Fraumene et al., 2003). Haplogroup U in particular, reaches 27.5% in Gallura, whilst it is only 4.4% in Barbagia. Haplogroup V seems to be present only in Barbagia with a high frequency (8.9%). Central Sardinia

(Barbagia) shows a strong discontinuity with Gallura for a higher frequency of haplogroup H, the presence of haplogroup V and a reduction of the frequencies of the other haplogroups. Barbagia, which appears to have just slight influences by Neolithic migration, has maintained ancient characteristics. Instead, Gallura is characterized by a more recent pattern of variability, as the absence of haplogroup V and the frequency of haplogroup U seem to demonstrate (Morelli et al., 2000). From this perspective, central Sardinia seems to maintain an Upper Palaeolithic mitochondrial background, sharing with the Iberian Peninsula the presence of haplogroup V and the highest incidence of haplogroup H (Morelli et al., 2000).

A recent research on the central-eastern area of the island (Ogliastra) (Fraumene et al., 2003) shows a differentiation of some frequencies between the area under scrutiny and the rest of Sardinia. The examined villages present a limited number of mitochondrial lineages, indicating a reduced female gene pool. Analysis on haplogroup H suggests to Fraumene et al. (2003) that the demographic expansion occurred between 12,500 and 2,900 years B.P. Moreover, the authors assert that the Neolithic population contributed to the present population more significantly, in contrast to the belief of other authors that suggest the prevalence of a Palaeolithic component (Falchi et al., 2006). An important result concerns haplogroup U, which reaches 31% in the village of Urzulei, with an average frequency in Ogliastra of 5.1%. This result is very similar to the frequency reported by Richards et al. (2000) for the whole Europe, the origin of which dated back to EUP, or about 50,000 years B.P.

In the present population of Sardinia, haplotypes whose origins clearly go back to beginning of the Upper Palaeolithic are still present, and from the analysis of table 1 emerges that a preponderant part of actual Sardinian haplotypes are of Palaeolithic rather than Neolithic origin. Analysis of haplogroups highlights the influence of the European south-western refuges during the Upper Palaeolithic on the structure of Sardinian mtDNA, also demonstrated by the haplotipic gradient 3.1G of chromosome Y (Malaspina et al., 2000). The analysis of the sequences of some Sardinian isolates compared with other Mediterranean populations (Falchi et al., 2006) confirms that most of the haplotypes coalesced in Palaeolithic times as a consequence of expansions from glacial refuges of south-western Europe in the last maximum glacial period.

Another interesting hypothesis emerges from the study of ancient mtDNA obtained by skeletal finds of Bronze age from different areas of the island and dated back between 1400 and 700 B.C. (Caramelli et al., 2007). Analysis revealed a strong internal homogeneity and a reduced variability of the sequences. The research shows the existence of a genetic continuity between Nuragic people that inhabited Sardinia during Bronze Age and the present day Sardinian population. But despite this continuity, there are differences between ancient and modern Sardinians, notably in their levels of internal differentiation, much higher in the latter. Moreover, the research highlighted a genetic similarity between the Nuragic people and the present Sardinian population from Ogliastra (central-eastern) that share three haplotypes with the ancient population. On the contrary, the modern population of Gallura (Northern Sardinia) appears genetically distant from both ancient and modern Sardinian samples, in agreement with the effects of relatively recent immigration from continental Italy that have affected Gallura more than Central and Southern Sardinia (Morelli et al., 2000). The research estimates that the time of coalescence of other Italian populations, such as the Etruscans, falls around 36,900 years ago.

Table 1. mtDNA haplotype frequencies in some Sardinian populations, compared with the frequencies of Europe

Restri	Haplogroups	Barbagia ^a	Gallura ^a	Ogliastra ^b	Talana ^c	Sardinia ^d	Europe ^e
-10394 DdeI -7025 AluI	H	64.4%	41.2%	56.6%	75.0%	38.4%	41.5%
-10394 DdeI	U,V,X	13.3%	27.5%	10.2%	10.0%	12.3%	22.5%
-16065 HinfI	J	2.2%	9.8%	18.3%	2.5%	5.5%	10.8%
-10394 DdeI +15606 AluI	T	8.9%	9.8%	12.6%	5.0%	11.0%	10.8%
+10028	I	0.0%	3.9%	2.3%	0.0%	2.7%	2.1%
-9052 HhaI	K	2.2%	5.9%	0.0%	0.0%	5.5%	8.3%
+10397 AluI	M	0.0%	0.0%	0.0%	0.0%	ND	0.4%
+10394 DdeI -8894 HaeIII	W	0.0%	0.0%	0.0%	0.0%	1.4%	1.2%
	Other	8.9%	2.0%	0.0%	7.5%	21.9%	2.4

^a : Morelli et al., 2000; ^b : Fraumene et al., 2003; ^c : Angius et al., 2001; ^d : Simoni et al., 2000; ^e : Torroni et al., 1996

Y Chromosome

The analysis of Y chromosome frequencies has allowed a deeper knowledge of the origins and evolution of humans. The variability represented by Y chromosomes is a unique document of the male history of anatomically modern humans and the relations among past populations (Scozzari et al., 2001). The numerous papers on polymorphisms of Y chromosomes that deal with Sardinia show some useful indications on genetic characteristics of the island and its settlement.

From a study on microsatellites of Y chromosome on several Sardinian samples (Ghiani and Vona, 2002), some results, such as the exceptionally high frequency of allele DYS19*17, confirm the peculiarity of Sardinians among Euro-Mediterranean populations. Haplotypes associated with allele DYS19*17 constitute about 16% of Sardinian haplotypes, whereas in Europe they represent a rare event. Moreover, the haplotypes carrying allele DYS19*17 have very different distributions in Gallura (9%), in Nuorese (55%) and in Campidano of Cagliari (36%), underlying the absence of internal genetic homogeneity. The internal heterogeneity is obvious also from the analysis of Y27H39, YCAII and YCAIII markers in samples from northern, central and southern Sardinia. The differentiation concerns not only the presence/absence of some alleles and the distribution of allele frequencies, but also the position of the samples within the genetic tree, which does not correspond with their geographic location (Latini et al., 1997).

Basically, Sardinians show the same haplotypes of the other European populations, but their peculiarity is due to the frequencies of some haplotypes (Semino et al., 2000). The haplotypes Eu18 and Eu19 represent 50% of European haplotypes. Eu18, whose frequency decreases from west to east in the Mediterranean, is characterized by M173 mutation, a Euro-Asian marker with an estimated age of about 30,000 years. In Sardinia, the frequency of M173 is around 23% (Francalacci et al., 2003).

Haplotype Eu7, with the mutation M170, derived by M89 that arrived from Middle East around 20,000-25,000 years ago, associated with Gravettian culture, is very frequent in the central part of eastern Europe, but it is present also among Basques and

Sardinians. Sardinians successively accumulated a mutation (M26) that differentiates haplotype Eu8 with frequencies of 35 %. Sardinians show a low overall frequency of haplotypes E and J relative to Italian populations. For example J-M172 in Sardinia has a value between 5% and 9.7% (Francalacci et al., 2003), against the frequencies of 16.7-29.1% of continental Italy (Semino et al., 2004).

According to Passarino et al. (2001) the frequencies of Eu7, Eu8 and Eu18 indicate that more than 60% of present Y chromosomes of Sardinians have a Palaeolithic origin and were brought by populations coming from Iberia, where these haplotypes show the highest variability and antiquity. The remaining haplotypes (Eu4, Eu9, Eu10 and Eu11), which originated in Middle East between 20,000 and 15,000 years ago, probably arrived with the Neolithic migrations. The successive isolation, for about 200 generations, and genetic drift influenced the different distribution of the frequencies even within the island.

The haplotype networks built with the combination of biparental markers and microsatellites of Y chromosomes in a great number of populations from Europe, western Asia and northern Africa (Malaspina et al., 1998), confirms the sharing between Sardinians and continental Europeans of the more widespread networks (1.1; 2.1; 3.1). Besides, network (1.3) seems a peculiarity of Sardinia, with frequencies varying between 39% and 41%. The same network has a frequency of 2% in the neighbour Corsica.

An analysis of Y chromosomes among populations from the western Mediterranean in comparison with some populations from north-eastern Europe and the Middle East highlights a decreasing cline in haplotype HG 9.2 from Middle Eastern to western, as a result of Neolithic diffusion (Scozzari et al., 2001). Chromosomes HG 9.2, which common ancestor dates back about 14,000 years ago (11,200–17,100), have in Sardinia very low frequencies. On the contrary, haplotype HG 2.2, while rare or absent in Europe, is extremely common in Sardinia with high frequencies (27–55%) in all parts of the island. HG 2.2 could have originated *in situ* after settlement of the island or arrived from a western European refuge occupied during the last glaciation. The presence of some HG 2.2 in Spain, Italy and France seems to support the last scenario (Scozzari et al., 2001). Even in this case, Sardinia appears differentiated from all the other

neighbouring regions and shows a certain internal variability. In fact, the frequency of the northern part of the island (Gallura) occupies an intermediate position between the rest of the Sardinia on one side and Corsica and the Italian continent on the other side. This situation could be an effect of the geographical position of Gallura and/or of the linguistic affinity with Corsicans.

Furthermore, the phylogenetic analysis of haplogroup I of Y chromosome reveals that subclade I1b2 of sub-haplogroup I1b* is scarcely represented in western Europe. Sardinians, with a frequency of 41%, Castilians (19%), Bearnais (Gascon, France) (8%) and Basques (6%) are some exceptions (Francalacci et al., 2003; Rootsi et al., 2004). According to the authors high frequency of I1b2 in the archaic area of Sardinia is explained by its presence in the first colonizers, who arrived, about 9,000 years ago. This heritage has been preserved by isolation and genetic drift.

Chikhi et al. (2002), revising Semino's data (2000) on several biallelic markers of Y chromosomes of different populations, highlight the clear outlier in Sardinians and Basques in comparison with European populations. These authors believe that Sardinians have a high proportion of genes derived from the Palaeolithic inhabitants of Europe. The differentiation of Sardinian populations is attributed to genetic drift, which acted on a Palaeolithic substrate shared by other populations and some input of Middle Eastern genes, rather than on a substrate created by an important Neolithic immigration to Sardinia. Therefore, about 60% of the Y chromosomes of the present day population of Sardinia might derive from migratory flows that occurred during the Upper Palaeolithic.

One study related genetic markers of Y chromosomes (biallelic markers, RFLP, and microsatellite) to the distribution and diffusion of Sardinian surnames (Zei et al., 2003). Many haplogroups of Italians and Europeans are represented in the pool of Sardinians' Y chromosome. Instead, the haplotype frequencies characterize Sardinians. Haplogroup R – M 269 represents 20.8% of Y Sardinian chromosomes, which is the lowest frequency in western Europe (50 – 80%). Haplogroup I – M 170 has the highest incidence (41.6%) among the western European populations, but lower frequencies among Sardinians, and it is characterized by haplotype 49a,f – Ht12, YCAIIa-21, YCAIIb-17 and DYS19-17. At first, this haplotype was indicated as a Sardinian marker

(Santachiara-Benerecetti et al., 1996; Caglià et al., 1997), but was later found also among Basques (Underhill et al., 2000), on the Iberian Peninsula, among the Bearnais (Bosh et al., 2001) and with low frequencies in Corsica and central-southern Italy. Haplogroup E (African origin), G and J (Near Eastern origin) have the same frequencies among Sardinians as other Mediterranean populations.

The distribution of haplogroups in Sardinia appears strongly heterogeneous. In particular the frequency of haplogroup G – M 201 is significantly higher in the north and the Haplogroup I – M 26 is more significantly represented in the central-eastern area, characterized by a reduced presence of haplogroup R – M 269. The sub-haplogroup I – M 26 appears heterogeneously distributed in relation to the ancestral collocation of surnames. The majority of surnames carrying this haplogroup seem to have arisen from the central-eastern area, including the archaic zone. The native populations retreated into this area during Phoenician, Carthaginian and Roman occupations. The subsequent isolation and genetic drift allowed an increase of haplogroup I – M 26 frequency, which in the north has a frequency significantly lower than expected. The isolation of the central-eastern area could also explain the distribution of other haplogroups. R – M 269 has a low frequency in the central area and a prevalence in the northern area, which suggests that it is likely to have arrived from the continent after the diffusion of I – M 26.

Discussion

Peopling

Lithic handmade objects dating back to the archaic Clactonian period in the Perfugas and Laerru areas of the north of the island suggest the presence of humans in Sardinia from the beginning of the Lower Palaeolithic period (Lilliu, 1998). Nevertheless, bones dating from the same period have not yet been found. In fact, findings indicate the presence of *Homo sapiens* between 20,000 and 12,500 years ago (Martini and Ulzega, 1990; Sondaar et al., 1995).

The most likely hypothesis of the settlement of Sardinia is that humans reached the Sardinian-Corsican block through a bridge that connected it with Tuscany because of modification during the Quaternary. This Sardinian expansion, ascribed by the

mtDNA, date to period between 27,174 and 78,234 years ago (Comas et al., 1997) with an average period of 52,083 years. Corsica and Sardinia were still one single block during the Recent Wurmian period (36,000-15,000 BC), and since the Corsican expansion was estimated to occur around 14,443–41,584, we could hypothesize the existence of two expansions, occurring successively, that could have taken place in the southern part of the block (Sardinia) and in the northern part (Corsica) (Varesi et al., 2000). They could have been favoured by the different orography of the two regions and by the diversity of the climatic conditions during the expansion period. The orographic and geographic conditions of Corsica, characterized by high mountains, produce colder periods in Corsica than in Sardinia. This is suggested by the moraine deposits of Quaternary ice in Corsica that indicate three glacial periods. The glacial Corsican periods correspond to the pluvial periods in Sardinia (Vardabasso Bonicelli, 1968). The less frigid climate may have drawn groups to the southern part of the block while the expansion in the northern part have occurred after the glacial cold had abated. The expansion of the population in Corsica could have happened by way of a migration from Sardinia, in particular from the northern area (Gallura). This hypothesis was strengthened by the genetic affinity between the two islands highlighted by the study of the classical markers (Vona et al., 1995; Moral et al., 1996; Memmi et al., 1998).

A second hypothesis of pathways of human settlement of Corsica and Sardinia during the Palaeolithic is through Liguria and southern France supported by some palaeontological data such as the discovery of the same kind of Palaeolithic handmade *tayaziana* facies in Liguria–Provence and in Sardinia (Lilliu, 1988). Also the analysis of mtDNA (Torrioni et al., 1998) suggests that haplotype V of mtDNA originated in a region between the north of Spain and the south of France. From this area it spread throughout Europe in various directions, including to Sardinia, which was probably still joined to Corsica.

Tobias (2002) proposed another hypothesis for the peopling of Sardinia. From some geographic, genetic and linguistic observations, as well as analysis of the distribution of fossil fauna he suggests that a possible path for the settlement of the island by *Homo sapiens* started from northern Africa. Sardinia would have been

therefore a gateway between Africa and Europe, and small groups would have moved bidirectionally through the island.

Several researches on the Y chromosome (Semino et al., 2000; Passarino et al., 2001; Chiki et al., 2002) underline the presence of a strong Palaeolithic component and a smaller Neolithic influence on the Sardinian gene pool. Therefore, it is very likely that during the Upper Palaeolithic period, Sardinia was the scene of a demographic expansion, even if the question of the arrival on the island of the mitochondrial DNA and Y chromosome haplotypes dating back to different Palaeolithic periods still remains to be cleared up. Nevertheless, it is not plausible that such a high proportion of Palaeolithic characteristics can be entirely attributed to Neolithic migrations.

Genetic variability and differentiation of Sardinia

From the review of the literature on Sardinian genetic characteristics two important concepts emerge:

- 1) The Sardinian population has a particular genetic structure compared with continental Italian, Mediterranean and European populations;
- 2) Sardinians do not constitute a homogeneous population from a genetic point of view. Compared to other European and Mediterranean populations, Sardinians are distinguished by genetic characteristics. Briefly stated, this scenario is supported by the existence of several genetic boundaries in Europe according to Barbujani and Sokal (1990) and to Vona et al. (2002) (Fig. 2).

Sardinians may constitute a unique pre-Indo-European population (Rickards et al., 1988). According to Contu et al. (1992), the present genetic composition of Sardinians is determined by the contributions of several ethnic groups of north-western Mediterranean, eastern Mediterranean and northern African origins inserted on a palaeo-Mediterranean substrate. Piazza et al. (1976) also suggested Middle Eastern origins, through the analysis of some immunoglobulin markers. Analyses of DNA markers, mtDNA and Y chromosome suggest Middle Eastern, western Mediterranean and northern African influences. Nevertheless, the contribution of various components to the present gene pool is still under discussion. It is therefore very difficult to recognize which groups or populations influenced the gene pool of the present

Sardinian population. The difficulty in identifying the different components is increased by an intrinsic internal heterogeneity. The geographer Tolomeo, during the 2nd century B.C., described the presence of numerous ethnic groups in Sardinia, with influenced areas clearly geographically delimited. The studies on internal genetic diversity suggest a fragmentation of the Sardinian population into numerous isolates. The differences emerging within the island have been attributed by most authors to genetic drift, which would be strongly active because of the natural boundaries (Workman et al., 1975). Terrenato et al. (1971) recognize in each Sardinian village a genetic isolate.

The demographic history of Sardinia has surely contributed to the development of random phenomena that are important for their genetic implications. It is obvious that the demographic history of Sardinia has been characterized by an extremely low population density. The general and the effective population underwent drastic decreases. For this reason, most of the researchers (Cavalli Sforza, 1994; Francalacci et al., 2003; Rootsi et al., 2004) indicate genetic drift as the main factor the genetic peculiarity of Sardinia and for internal differentiation. The effects caused by drift remained ordered in time because the Sardinian population had experienced great isolation with respect both to Mediterranean populations and within the island itself. The matrimonial structure clearly suggests this isolation. The average matrimonial distance with respect to the places of birth of husband and wife shows higher values for the plain and the coastal hills, while lower values are found in the mountains. Analysis of endogamy in several villages of the central-eastern area (Vona et al., 1996) shows that the rates of endogamy from 1800 to 1980 were high, in some periods reaching over 90%. Matrimonial distances remain constantly reduced, usually less than 10 km reaching the highest values of about 15 km for marriages between Sardinians and 60 km for marriages between Sardinian and continental Italian partners (1956 – 1980).

In the central-southern area of the island between 1695 and 1825 the average endogamy value was 65.3%, with peaks at 70.0%. Despite this not-so-high mean endogamy rate, the matrimonial distance between the places of origin of the spouses of exogamic marriages is 6 km and does not present relevant changes over time. Even the average of the distance between the place of birth and the place of marriage has a value of 6.2 km with a range of 4.3–8.3 km, indicating little internal mobility (Gatti, 1990).

The matrimonial area, and therefore genetic exchanges, appeared very limited.

A further indication of isolation comes from the study of blood marriages. Consanguinity in Sardinia has been studied by Moroni et al. (1972). On the whole, for all the period under scrutiny (1765-1969), the average coefficient of inbreeding ($\alpha = 1.5446 \times 10^{-3}$) and the frequency of consanguineous marriage (4.44%) are not very high. The α coefficient and the percentage of consanguineous marriages vary in time with maximum peaks of 3.3325 (1920–24) and of 12.36% (1870–74), respectively. The trend of consanguinity does not appear uniform in the territory with variations according to altitude and to the historical–geographic areas. The coefficient increases with the rise of altitude and the distance from the coasts (Moroni et al., 1972). The historical–geographic areas show a strong differentiation, since some of them have a very high consanguinity volume, that remarkably exceeds the average values, and others have low consanguinity values. Some villages of the central area of Sardinia show, even in recent times, a high volume of consanguinity (Vona et al., 1996) with average frequencies of the consanguineous marriages between 17% and 20% for the period 1806–1980 and with some peaks of around 35%. The α coefficient has average values of between 3.71 and 4.69×10^{-3} . Despite the general trend in the passing of consanguineous marriages, in some villages the two parameters continued to have significant values between 1956 and 1980. The biological and demographic history of several villages, in particular in the interior of the island, for a long time was signified by strong endogamy and by a high rate of inbreeding due to their isolation.

Conclusion

Several researches suggest that Sardinians have a peculiar and differentiated genetic structure. Even though many groups of different origins arrived in Sardinia throughout its history, it was isolated for a long time in two ways: from Italian and Mediterranean regions, and between geographical and cultural areas of the island itself. The Sardinian population turned out to be an example of genetic isolation among Italian, European and Mediterranean populations. The genetic differentiation could be due to the long period of prehistoric and historic isolation of Sardinia. The reason for this isolation can be outlined as follows:

- 1) Geographical position and insularity: Sardinia is the Mediterranean island furthest from continental shores and this does not favour vast migrations and great transfers, limiting external genetic and cultural contributions;
- 2) Internal geographical conditions: tectonics created barriers between communities, thus fragmenting the population and hindering the relationships.
- 3) The dimensions of the island: it is oversized compared to the number of inhabitants. In fact, genetic drift and isolation from outside countries, together with the relatively small amount of internal migration, led to the differentiation and the independent evolution of the Sardinian regions, which differ from historical, cultural and linguistic points of view. Moreover, high values of endogamy and consanguinity, observed in several villages, contributed to increasing the inner differentiation of the island (Vona et al., 1996). The presence of malaria, endemic until its eradication in 1948, was a selective factor that directly influenced the distribution of some genes, whose frequencies characterize Sardinians.

All these factors, together with prehistorical and historical events, have contributed to the remarkable genetic differentiation of Sardinians from other European and Mediterranean populations, as demonstrated by the well-documented uniqueness of some gene frequencies (Piazza et al., 1976; Vona et al., 1994; Modiano et al., 1986), and by the microgeographic heterogeneity within the island (Vona et al., 1992).

The general observation that can be drawn from researches on the Sardinian population is that it was influenced by the migratory phenomena that characterized the Euro-Mediterranean area during both Palaeolithic and Neolithic periods and during subsequent historical periods. However, these possible influences of different populations were limited and combined in a particular ensemble for the reasons explained above.

Finally, as Passarino et al. (2001) has noted in isolated populations, such as Sardinia, characterized by peculiar frequencies for several polymorphisms, understanding the origins and establishing the prevalence of the different components that constitute the present gene pool can be very difficult.

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