

# Matrilineal Heritage in Southern Iberia Reveals Deep Genetic Links between Continents

Candela L. Hernández and Rosario Calderón

Departamento de Zoología y Antropología Física, Facultad de Biología, Universidad Complutense, Madrid, Spain

## ABSTRACT

*Within the Mediterranean Basin, the Iberian Peninsula has been a focus of attraction for several cultures and civilizations from its prehistory and history, making it a target territory for studying human migration patterns and peopling processes using a wide and heterogeneous spectrum of genomic markers. While its Cantabrian fringe represents the most regularly analysed area in terms of its mitochondrial diversity, the absence of monographic surveys on the maternal genetic composition of southern Iberians (i.e., Andalusians) is striking. In this work, we present a comprehensive view of various aspects of the human maternal heritage of the autochthonous Andalusian population regarding specific mitochondrial haplogroups considered key candidates to determine the genetic relationship between Europe and Africa. Data reveal that southern Iberian populations do not have genetically homogeneous mitochondrial DNA profiles, and their observed genetic affinity with north-western African populations represents strong signals of old, sustained and bidirectional human movements between the northern and southern shores of the western Mediterranean. Thorough analyses of African mtDNA haplogroups have shown that the most relevant African contribution within Iberian Peninsula could be explained as a consequence of prehistoric events. The subsequent historic episodes helped to strengthen the ties between both shores. In southern Iberia, mitochondrial and other genetic markers show that the Strait of Gibraltar together with its surrounding maritime areas should be considered a bridge between continents. More broadly, the Mediterranean Sea has acted as a transport surface, that is, as a permeable barrier to human migrations from prehistoric and historic times. In conclusion, this research contributes to our knowledge of processes that have shaped the recent human genetic history in the Mediterranean and, more specifically, of the population dynamics that the inhabitants of southern Iberia have experienced with respect to other neighbouring North African populations.*

**Key words:** Andalusia, Northern Africa, mtDNA, gene flow, Mediterranean space

## Introduction

Since the 1980s, scholars have tried to resolve key questions about the human evolutionary past by analysing mitochondrial DNA (mtDNA) and the non-recombining region of the Y chromosome (NRY)<sup>1</sup>. The sexual specificity defined by uniparental inheritance patterns implies that the markers in these genomic regions record demographic and population processes that are specific to women and men, respectively. Furthermore, given that mtDNA and NRY escape homologous meiotic recombination, haploid markers allow the estimation of coalescence times (time to most recent common ancestor, TMRCA) and population phylogenetic inferences<sup>2,3</sup>.

MtDNA comprises only a tiny fraction of the total human genome [ $<0.001\%$ ]<sup>4</sup>, yet it is frequently used as a mo-

lecular tool for analysing the genetic diversity of contemporary and ancient human populations. This matrilineal molecule has some interrelated features that justify its broad range of applications. New mitochondrial variants arise more frequently than expected (because of a high mutation rate) and are more affected by the genetic drift process (due to the lack of recombination and low effective size,  $N_e$ )<sup>1,5,6</sup>. Consequently, different mitochondrial lineages—or haplogroups—evolve independently from one other in a population by the sequential accumulation of mutations, enabling reconstruction of the phylogenetic relationships among them<sup>7</sup>. However, the high evolutionary rate of the mtDNA molecule is not homogeneous. The human mitochondrial genome is mostly (~90%) composed of coding regions, whereas the remaining fragment—the ‘control region’—has a higher mutation rate

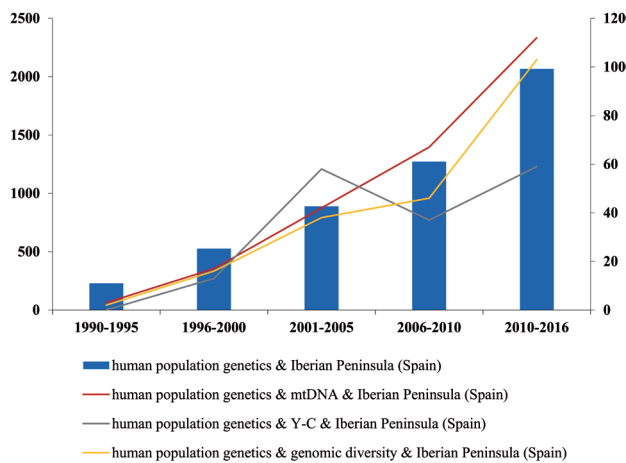


Fig. 1. Temporal trends (~25 years) in the number of publications on human genetic diversity in the Iberian Peninsula (Spain). Data are based on selected keywords in the PubMed database.

than the former. The control region is heterogeneous in this respect because it harbours some hotspots of variability (such as the hypervariable segment I or HVS-I). The polymorphic nature of the control region has been in the spotlight for mitochondrial genetic diversity studies<sup>8</sup>. Nevertheless, forensic genetics has demonstrated that the control region cannot be used for discrimination, especially when analysing the most common mitochondrial variants<sup>9</sup>. There are signals that indicate the strong effect of purifying selection on the mitochondrial genome, removing the most deleterious mutations<sup>10,11</sup>. In this context, the human mtDNA phylogeny tends to show a higher proportion of synonymous mutations in its older branches. That is, the dN/dS (ratio of nonsynonymous, dN, to synonymous mutations, dS) is lower in African than in European sequences, implying that the mutation rate slows down backwards in time for mtDNA phylogeny, and, therefore, a violation of the molecular clock. Another consequence of the high evolutionary rate associated with mtDNA is the well-known homoplasy phenomenon: the presence of recurrent mutations in human mitochondrial phylogeny. These convergent mutation events could create phylogenetic ambiguities that lead to the possibility of inferring different branching orders for the same set of sequences<sup>3</sup>.

Methodological strategies for analysing mtDNA have evolved rapidly, allowing a critical increase in the phylogenetic resolution. The first restriction fragment length-based approaches<sup>12,13</sup> were followed by the sequencing of hypervariable control regions<sup>14–16</sup>, and then by the analysis of some informative coding region positions<sup>17</sup> and/or multiple typing of them<sup>18,19</sup>. Likewise, in the last years, the study of whole mitochondrial genomes (»mitogenomes«) has provided a detailed phylogenetic classification of mtDNA sequences, the detection of diversity patterns previously overlooked or unknown, and an evaluation of the role of evolutionary factors that shape the demographic histories of well-defined human populations. In fact, these new

sequencing technologies have allowed us to overcome the limitations that are associated with traditional Sanger approaches. Mitogenome studies mainly focus on the dissection of specific mitochondrial lineages<sup>20–24</sup>.

## The Iberian Peninsula from a matrilineal genetic perspective

Within the Mediterranean Basin, the Iberian Peninsula is considered a target territory for human population genetic studies. The Peninsula has a strategic geographic position, being the closest connection between Europe and Africa, and it is geographically distant from the foci where the two most important events in recent human evolution occurred: the out-of-Africa migration of modern *Homo sapiens* and the introduction of agriculture. Iberia is also assumed to be the main southern refuge during the Last Glacial Maximum (LGM)<sup>25</sup>.

Figure 1 presents statistics on the number of studies published on human genetic diversity in Iberia, with special reference to Spanish populations. Between 1990 and 2016, a continuous increase in the number of publications is observed and, curiously, the study of mtDNA variation seems to show a growing scientific interest with respect to the Y chromosome, with the latter having an even more erratic profile. The number of studies that analyse the extent and nature of human genetic diversity in both mainland and insular Spanish populations has notably increased in the last five years (2010-2016). This fact can be explained by the implementation of new sequencing and massive genotyping technologies. Therefore, a large amount of genomic data is currently available in various population samples and territories of Spain. Nevertheless, familiar origins of characterized samples do not exhibit a homogeneous geographic distribution across the national territory.

The first studies on matrilineal diversity in Iberian populations were performed in northern Spain, and, more specifically, in the Basque Country. Mitochondrial DNA variation in Basques has consistently shown low diversity levels and peak frequencies of haplogroup H, the most frequently detected clade in Europe. These findings have allowed the Basque mitochondrial profile to be distinguished from other European populations<sup>16,26</sup>. Using high phylogenetic resolution procedures, more recent genetic studies of mtDNA in Basques from Spain have supported the previously noted low genetic variability as well a significant intrapopulation heterogeneity<sup>27</sup>. The latter scenario seems to be caused by population fragmentation due to local isolation and limited gene flow<sup>28,29</sup>.

Other Iberian regions, including Galicia, located in the northwestern end of the Cantabrian cornice, and the adjacent regions of Asturias and Cantabria –in the intermediate Cantabrian littoral– have also been extensively studied from a matrilineal perspective<sup>29–34</sup>. Galicians share similarities with Spanish Basques in both their high frequency of H haplotypes and their low levels of mitochondrial diversity<sup>33</sup>. Its autochthonous population is

also distinguished by deeply rooted socio-cultural traits<sup>35</sup>, and interestingly, is tied to an influence of maternal lineages linked to the African continent. For example, sub-Saharan macro-haplogroup L has frequencies between 2.5 and 3.0% in the Galician total mitochondrial variability<sup>34,36</sup>. There is also a relatively high representation (2.2%) of clade U6, which is traditionally associated with North Africa. Within the Iberian Peninsula, African mtDNA lineages have been more frequently detected in Portugal<sup>37</sup>. These findings and other recent observations highlight the relevance of the Iberian Atlantic façade in the assimilation of genetic variants from the neighbouring continent. Correspondingly, an interest in analysing the Canary Islands has been centred on its insular character and its closeness with Africa<sup>38–40</sup>. Its mitochondrial variation shows a strong influence from North Africa based on the presence of a specific U6 sub-branch (i.e., U6b1a). This sub-branch is considered a Canarian autochthonous radiation and it is a signal of the initial settlement of this archipelago<sup>38</sup>.

Andalusia, located on the southern end of the Iberian Peninsula, is a geographically extensive region of Spain, comprising ~20% of its total land area. Andalusia has been densely populated since ancient times and has a long, rich history of migrations, preferentially across the Mediterranean. Andalusia is the only Spanish region with coasts belonging to two seas, the Mediterranean and the Atlantic. Its Mediterranean character has favoured the inclusion and the continuous interaction with cultures that were the cradle of the western civilization. Its Atlantic side ensured a leading role in the discovery and colonization of the New World. Andalusia is also a natural bridge between Europe and Africa, with the Strait of Gibraltar being ~14 km wide.

Despite these interesting characteristics, the composition and genetic structure of the Andalusians was not analysed in depth until the early 2000s. In this context, Andalusia seems to have been overshadowed by the leading role of populations that settled along the Cantabrian fringe of northern Spain. However, recent observations about the Andalusian gene pool, such as the presence of remarkable African genetic signatures in well-defined areas and populations within the region (see below), have significantly driven studies on Andalusian genomic diversity. These approaches aimed to evaluate evidence on the age of human movements across the Strait of Gibraltar and its neighbouring maritime areas.

High levels of genetic diversity have been systematically associated with the Andalusian maternal heritage. Côte-Real et al.<sup>41</sup> showed that the highest mean number of mtDNA pairwise differences among Iberian, Italian and North African sequences correspond to Andalusia. Later, Larruga et al.<sup>42</sup> highlighted that the Andalusian population harboured a notable African influence, namely the haplogroups L and M1 together with „Neolithic” traces, defined by clades J, T1 and U3. Casas et al.<sup>43</sup> analysed the mitochondrial diversity in modern and medieval samples with specific familiar origins within the Córdoba province, a historic territory located in inland Andalusia. This study allowed the detection of a fair contribution of

sub-Saharan lineages (L) and, conversely, an unexpected lower contribution of North African U6 clade.

Currently, the maternal heritage of Iberian populations is being studied with complete mitochondrial genomes. This approach usually focuses on a high-resolution analysis of candidate lineages to thoroughly define their internal diversification. Therefore, they provide phylogeographic and phylogenetic inferences with great potential to assess the underlying particularities of a population's demographic past. For example, Spanish Basques were selected to dissect certain autochthonous mtDNA clades. The results included U8a<sup>44</sup>, U5b1f, J1c5c1 and V22<sup>45</sup>, HV4a1a<sup>46</sup> and certain branches of haplogroup H (H2a5<sup>36</sup>, H1j1, H1t1, H2a5a1, H1av1, H3c2a, and H1e1a1<sup>23</sup>).

Similarly, the presence of African mitochondrial lineages in the Iberian Peninsula (L, M1 and U6) has also been evaluated with high-resolution techniques. Cerezo et al.<sup>47</sup> analysing macro-haplogroup L in Europe, provided evidence of transcontinental movements that were not exclusively restricted to the Muslim invasion of Iberia. Likewise, members of L3f sub-clade have been detected among Asturians, who are close neighbours of the Galician population. Their presence has also been interpreted as a consequence of deep temporal connections between Iberia and North Africa<sup>48</sup>. Other recent haplogroup U6 studies<sup>49,50</sup> account for the history of this clade in a broader geographic context than Iberia and use this clade as a key marker in population interchange processes between Europe and Africa.

### **New data on the human maternal heritage in southern Iberia**

The maternal legacy of Andalusians was recently analysed and published by Hernández et al.<sup>51,52</sup>. Within the region, research has been conducted on two distant and well-differentiated territories: Huelva province, located in the western extreme, bordering Portugal, and Granada province, on the eastern side, and characterized by a long-lasting Muslim presence (see Figure 2). It is worth noting that both Andalusian sub-populations are coastal and that they record significant and interesting differences in their historic and demographic past.

The mitochondrial profiles of 750 autochthonous and unrelated individuals (280 from Huelva and 470 from Granada) have been studied by our team. Criteria for sampling strategies guarantee that these samples are representative of the abovementioned Andalusian territories (further details in our publications<sup>51,53</sup>). The main results were as follows: *i*) High levels of mtDNA diversity were observed in both western (Huelva) and eastern (Granada) Andalusia. These findings contrast with observations from other regions and populations in the Iberian Peninsula, *ii*) Analysis of mtDNA sequences by mismatch distributions and neutrality tests<sup>51</sup> showed that both populations have experienced episodes of recent population expansions. These results significantly differ from those found in northern Iberia<sup>27,29,33</sup>, *iii*) Both global mtDNA diversity<sup>51</sup> and diver-

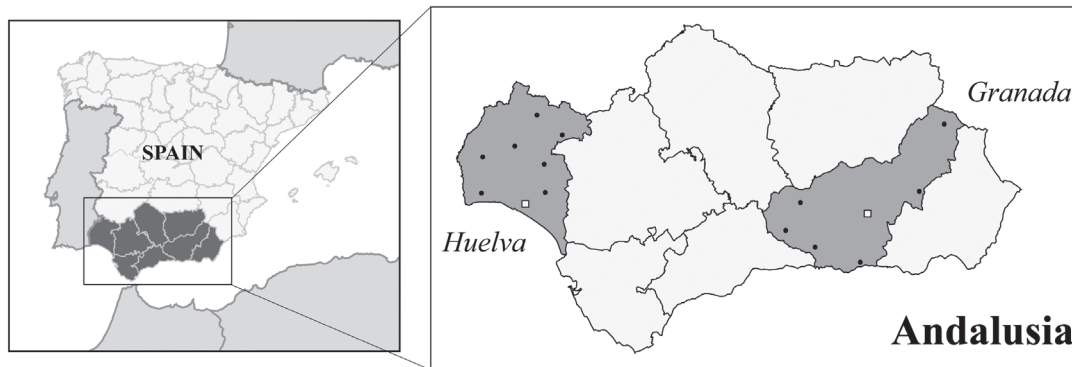


Fig. 2. The Andalusian region and Huelva and Granada provinces in the Iberian Peninsula. The 13 sampling localities are highlighted with points. The capital cities of each province are shown with white squares.

sity in specific maternal lineages<sup>52</sup>, Hernández et al. unpublished data demonstrated geographic micro-differentiation. Populations from western and eastern Andalusia are characterized by a broad spectrum of mitochondrial haplogroups that present opposite and, to a certain extent, supplementary patterns. Whereas the western population from Huelva have a relatively high frequency and great diversification of African lineages (U6 and L), the autochthonous population from Granada province is distinguished by higher levels and internal diversity of haplogroup H, the European clade par excellence (see Table 1). Our more detailed phylogenetic analysis in Andalusia provided valuable information about the extent of the genetic relationships between Europe and Africa.

TABLE 1

AFRICAN LINEAGES AND CLADE H MTDNA STRUCTURE IN ANDALUSIA. ONLY THOSE H SUB-HAPLOGROUPS THAT WERE RECORDED AS >2% IN AT LEAST ONE OF THE POPULATIONS ARE SHOWN.

	Western Andalusia (Huelva)	Eastern Andalusia (Granada)
$N_T$	280	470
<b>African lineages<sup>1</sup></b>	<b>33 (11.79%)</b>	<b>17 (3.62%)</b>
U6	21 (7.5%)	7 (1.49%)
M1	1 (0.36%)	3 (0.64%)
L	11 (3.93%)	7 (1.49%)
<b>Clade H<sup>2</sup></b>	<b>110 (39.29%)</b>	<b>227 (48.30%)</b>
H1	48 (17.14%)	73 (15.53%)
H3	16 (5.71%)	41 (8.72%)
H4	3 (1.07%)	12 (2.56%)
H5	5 (1.79%)	17 (3.62%)
H6	8 (2.86%)	16 (3.40%)
other H	30 (10.71%)	68 (14.47%)

<sup>1</sup> Data from<sup>52</sup>

<sup>2</sup> Hernández et al. unpublished data

### Andalusia as a bridge between Europe and Africa: mitochondrial diversity

For studying transcontinental migrations within the western Mediterranean, research studies have focused on scanning H lineages to detect north-south migrations, and U6 and L lineages for the opposite direction. This scenario assumes that all of these mitochondrial haplogroups are good proxies for the ancestry of each side (coast) of the Mediterranean space<sup>52</sup>.

Figure 3 depicts the geographic variations of mtDNA African lineages U6, M1 and L (Fig. 3A) and haplogroup H (Fig. 3B). The contour maps not only reflect distinctive spatial patterns but also show the key role that the Iberian Peninsula might have played in the successive spreading of African genes towards the rest of Europe, as well as the radiation of other genetic signals towards their neighbours in the southern Mediterranean. In this sense, matrilineal legacy in the western extremes of the Mediterranean has shown that Iberia should not be only considered as a sink but also as a source population.

Population genetic studies are largely convergent in highlighting the Iberian Peninsula as the European territory that harbours the most intense African traces, with a stronger influence on its southern side<sup>47,51</sup>. The relatively high record of maternal African lineages in western Andalusia is enriched by the detection of relevant sub-clusters inside clade L (L1b, L2a and L2b) and the vast internal diversification of haplogroup U6 (U6a, U6b and U6c)<sup>51</sup>. Interestingly, this picture contrasts with a rather weak African maternal signal in eastern Andalusia (Granada population); this fact cannot be easily interpreted from a historical perspective. The Kingdom of Granada (which lasted until the end of the 15th century) extended the Muslim domination of Andalusia for two and a half centuries longer than in the rest of the Peninsula<sup>53</sup>.

The phylogenetic analysis of African mtDNA lineages in Andalusia has further revealed the interesting position of western Andalusians (from Huelva) inside L1b and U6a basal nodes (see Fig. 4 in<sup>51</sup>). These findings led us to propose: *i*) The early arrival of these clades to the Iberian Peninsula, and *ii*) The hypothesis of an *in situ* origin of

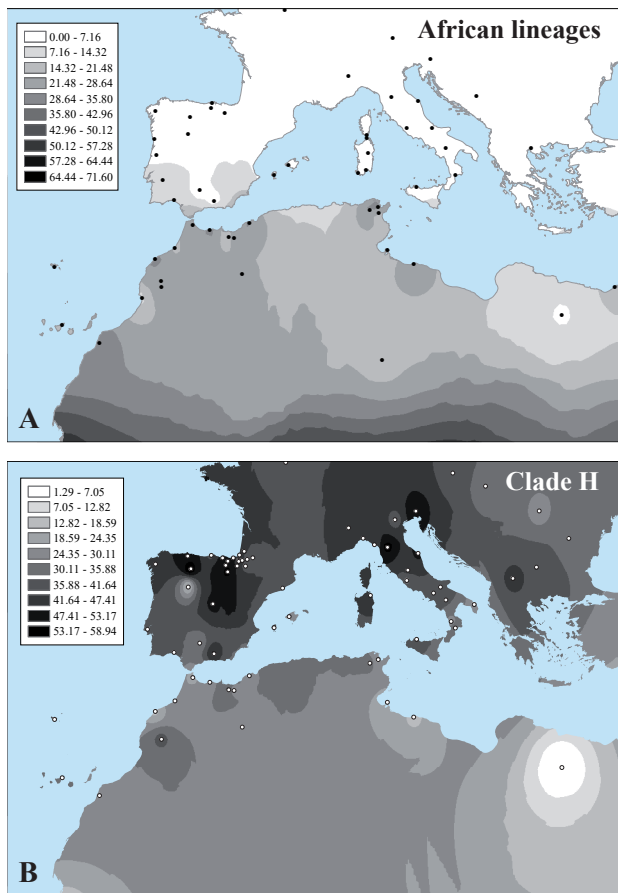


Fig. 3. Interpolation frequency (%) maps of A) African haplogroups –U6, M1 and L– and B) clade H. Population and data used for map construction can be found in <sup>52</sup>Hernández et al. unpublished data.

some U6 sub-branches in Iberia that led to re-expansion into North Africa. Recently, our team has also explored the complete sequencing of haplogroups U6, M1, L1, L2 and L3, which are present in the two Andalusian sub-populations<sup>52</sup>. The mitogenomic results indicated that the population relationships between Europe and Africa are

more ancient than previously thought (from the early Holocenec times) and that these gene flow episodes were not sporadic or punctual. Other studies of Iberian mtDNA diversity –using both ancient and modern mtDNA samples– have provided similar data and results, indicating the existence of old migratory episodes prior to the Muslim invasion<sup>47,48,54</sup>.

The mtDNA candidate sub-haplogroups U6a and L1b are used to assess gene flow from North Africa through Iberia. This statement is supported by analysis of human maternal heritage in Andalusia. Given the evolutionary ages and geographic distributions of lineages such as U6a1, L1b1a6, L1b1a8, L1b1a12 and pre-L1b1a16, we have proposed that some branches of U6a and L1b could have evolved within Iberia after a prehistoric introduction from Africa. Based on this assumption, the Maghrebi samples that are interspersed among these sub-clades would represent signals of back-migrations to Africa from Iberia. Similarly, Europeans included in these clusters further indicate Iberia as the main entrance gate of African lineages and their subsequent dispersion on the European continent.

Moreover, an intertwined evolutionary history between both shores of the western Mediterranean can also be inferred from analysis of clade H (Hernández et al. unpublished data), which reaches ~40-50% occurrence, on average, in the Iberian Peninsula. Lineage H is the most frequently detected European haplogroup within North African populations (see Fig. 3B), with a remarkable negative W-E gradient along the Maghreb [Morocco (38%<sup>55</sup>) to Egypt (14%<sup>56</sup>)]. High resolution analyses of clade H in North African samples have enabled detection of notable local diversification as well as the presence of native H sub-branches<sup>57,58</sup>.

Analysis of the internal structures of the major sub-clades H1 and H3 reveals parallelisms between Iberian and North African populations. Phylogeographic and phylogenetic analyses performed by this team in western and eastern Andalusian samples (Hernández et al. unpublished data) further support massive population movements from Iberia to Maghreb –after the LGM– that carried H1 and H3 haplogroups<sup>57–59</sup>. The North African fringe

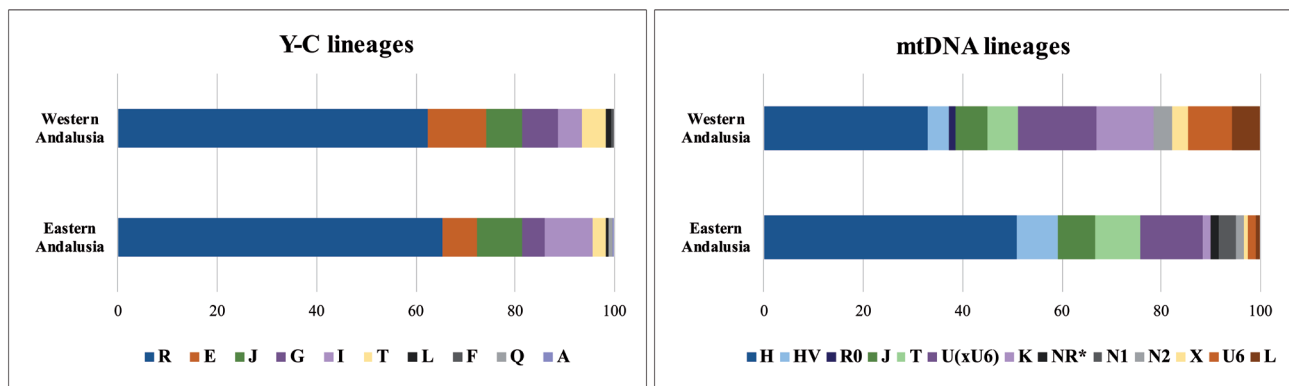


Fig 4. Types and frequencies (%) of paternal and maternal lineages in western and eastern Andalusia.

would have been the southernmost extreme of those post-glacial expansions that repopulated the rest of Europe with origins in the Iberian Peninsula<sup>60,61</sup>.

Early bidirectional movements between Iberia and Africa required maritime crossings and, hence, the use of ancient navigation techniques in the Mediterranean, one of world's earliest *foci* of maritime activity<sup>62</sup>. Longer maritime routes, used for the exploitation of littoral resources, were not established until the Neolithic era<sup>62,63</sup>. Results based on various polymorphic markers and genomic regions in western Mediterranean populations also indicate recurrent migrations across the Strait of Gibraltar and surrounding areas. These migrations coincided with the timing of high maritime activity. The ancient, frequently rejected, bridge connecting the Maghreb and Andalusia would have had a pier on the small island of Alborán<sup>52</sup>. Along these lines Currat et al.<sup>64</sup>, have suggested that the genetic profiles of human populations surrounding the Strait of Gibraltar could reflect an ancient genetic structure which has not been completely erased by more recent events, such as the Neolithic transition.

In addition to other evidence such as the close similarities between Epipaleolithic industries –the Magdalenian in Spain and the Iberomaurusian in Northwest Africa (~20–12.9 ky cal BP)<sup>65,66</sup>– other authors have highlighted contrasting matches in the Neolithisation process between southern Iberia and the Maghreb. For instance, it has been proposed that the initial establishment of the Early Neolithic in southern Iberia would have likely had a northern African origin. This hypothesis was based on ceramic ornamental similarities among Neolithic sites in Oran, the eastern Rif and Andalusia. It is also based on instruments made of human bones in the Nerja cave (Málaga) and the Maghreb. Lastly, this hypothesis is supported by the use of the same species of domesticated animals<sup>67</sup>. Therefore, some particularities associated with a southern Iberian »Neolithic package« could not be explained by a Mediterranean influence; they may be the result of assimilation from the African continent<sup>67,68</sup>. In addition, the synchronic development of the Neolithic in Andalusia and North Africa, and the coincident appearance of Neolithic features in southern Spain and northern Morocco, do not show a temporal gradient from Europe to northern Africa<sup>66</sup>. Instead, these observations suggest a rapid Neolithic expansion model, favoured by the use of maritime technology and trade networks that were previously established<sup>67</sup>.

Several political, sociocultural, and economic links have tied the northern and southern shores of the Strait of Gibraltar in protohistoric and historic periods<sup>69</sup>. These connections were especially intense due to the shared political and administrative rule of Iberia and the Maghreb during the Roman Empire and the Muslim conquest. All described scenarios, including those drawn from genetic data and those from prehistoric and historic evidence, have proposed that the westernmost end of the Mediterranean, covering the Strait of Gibraltar and the Alborán Sea, was not considered as a barrier, but a crossroad between the two landmasses<sup>51,69</sup>. In this context, northwest

Africa and Iberia would represent a unique and autonomous space, in a scenario that anthropologist G. Freyre describes as a »bi-continent«<sup>70</sup>.

Although side-to-side human movements have occurred recurrently in the western Mediterranean, different demographic histories would have determined assimilations of genes in each direction. The weight of the continental-specific mitochondrial traces –U6 and L for Africa and H for Europe– detected on the opposite coasts of the Mediterranean, is not equivalent. The strong signal of European markers in North Africa when compared to the African influence in Europe would reflect a more intense southward gene flow and/or a more distinctive demographic processes in southern Europe and North Africa<sup>71,72</sup>. Spatial dynamics and the demographic past of populations must be considered when trying to explain the present human genetic structure<sup>73</sup>.

### The diversity of southern Iberia from other genetic markers

The Andalusian population is also being studied with other genomic markers. The results provided by the NRY, albeit not completely comparable to mtDNA profiles, show parallel features. For both uniparental systems, Andalusian populations from western and eastern sides of the region are characterized, as expected, by a western European genetic background, with high frequencies of mtDNA haplogroup H (40-48%) and Y-chromosome (Y-C) haplogroup R-M269 (~60%)<sup>74</sup>. Calderón et al. unpublished data. For the sake of comparisons, Figure 4 shows the composition of patrilineal and matrilineal lineages in Andalusians.

Some interesting radiations have been detected within Y-C clades E and J. An example is found in the haplogroup E-M81, commonly known as the 'Berber marker.' Frequencies of E-M81 in Andalusia (~3.3% as average) do not seem to be concordant with the regions in which Islamic occupation was the most intense and prolonged. This result would strengthen the idea that human movements between Maghreb and Iberia were not only restricted to this historic period. Other patrilineal markers, such as E-M78 and E-V13, were mainly observed in western Andalusia, and could be associated with an increasing gene flow related to trade and exchange networks that were established with the Kingdom of Tartessos (ca. 800-540 BC)<sup>75</sup> in southwestern Iberia<sup>76</sup>. Interestingly, some J sub-clades have been linked to an Arab presence in the Iberian Peninsula during the Islamic expansion (J1), as well as to the Greek and Phoenician colonies involved in commerce activities (J2)<sup>53</sup>. These findings illustrate the existence of relevant male gene flow with populations from other Mediterranean areas.

The main differences detected regarding the mtDNA and Y-C profiles in Andalusia are grounded in the genetic continuity *vs.* discontinuity along the territory, as well as in the differential assimilation of African genes. The remarkable African maternal influence in western Andalusia (Huelva) is not as strong for the Y-C markers. The di-

vergence found in both human haploid systems has been explained by intrinsic differences in migratory and reproductive behaviour between sexes<sup>77,78</sup>. Several studies have noticed a higher diversification between continental areas for Y-C variation when compared to mtDNA patterns<sup>79</sup>. These observations have been regularly interpreted as a consequence of a higher female than male migration rate<sup>78</sup>. Thus, the genetic barriers between populations would not have been so insurmountable for maternal lineages. However, there are also other factors that would have contributed to this scenario, such as differences in the effective population sizes ( $N_e$ ) of the sexes linked to the variance in reproductive success due to phenomena such as polygyny<sup>77,80</sup>.

In addition to the non-recombining genomic regions, our team has also paid special attention to the analysis of some other relevant autosomal markers in southern Iberia. Human immunoglobulin allotypic variations displayed a typical European *GM* component that was enriched by the presence of the sub-Saharan *GM\*1,17 5\** haplotype. This marker is similarly represented (~4%) in southern (Andalusia<sup>81,82</sup>) and northwestern (Galicia<sup>83</sup>) Iberia. These peninsular areas recorded a highly uneven Muslim influence; hence, we have explored other hypothesis to explain this genetic parallelism, such as the SW-NW connection of Iberia by means of the Roman *Vía de la Plata*. The historic road enabled military and commercial activities and it could have also been a vehicle for the spread of genes<sup>51</sup>. Lastly, we have studied the molecular variation of apolipoprotein E (apoE) in Andalusia. The frequencies of the  $\epsilon 4$  allele in southern Iberia—higher than expected, given its spatial location and the well-established European gradient for this marker—would also point to multiple migration episodes experienced by the territory<sup>83</sup>.

It is noteworthy that, similar to the paternal heritage, these autosomal markers do not reveal genetic heterogeneity in southern Iberia. Therefore, the female population history is the responsible for uncovering micro-geographic differences between both ends of Andalusia.

### Future approaches and new perspectives

Andalusia is considered a crossroad and a gateway to several cultures, especially those settled around the Mediterranean. Hence, its autochthonous population is currently receiving preferential attention for understanding its genomic diversity, both neutral and that driven by se-

lection. In this context, population studies are being directed at a new experimental step, thanks to the analysis of high-density SNP panels by means of genome-wide (GW) screenings. The use of these methodological approaches, together with sophisticated computational treatment of genomic markers, permits assessment of the extent of interpopulation relationships, admixture and sub-structuring<sup>84</sup>. Furthermore, GW scans can also be used to explore genomic inbreeding in concrete populations, the reconstruction of regional ancestry<sup>85</sup>, the evaluation of selection signals in the human genome<sup>86</sup> and the role played by disease variants in population linked to specific territories<sup>87,88</sup>.

European studies have manifested an appreciable sub-structuring, with significant north-south genetic differences<sup>89–92</sup>. This structure demonstrates that, at the continental level, the European population would have undergone different demographic histories, retaining several distinctive cultural behaviours with respect to mating patterns between relatives (consanguineous phenomenon). The southernmost extreme of Europe—the Iberian Peninsula—is a key area for the application of GW procedures. According to Auton et al.<sup>93</sup>, southwestern Europe harbours the highest levels of genomic diversity, a fact that could reflect a substantial contribution from the African continent (a hypothesis that fit our mtDNA data, see above) and/or a structure dating back to the post-glacial constriction-expansion episode. As we have shown here, the distribution of some genetic variants—such as specific mtDNA lineages—in current human populations testify to past gene flow and migration events with defined directions and demographic consequences.

In summary, the inferences drawn from uniparental and autosomal markers, together with massive GW screenings, are revealing the central position of Andalusia as a hotspot for human genetic diversity on a Mediterranean and a European scale.

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R. Calderón

*Departamento de Zoología y Antropología Física, Facultad de Biología, Universidad Complutense, Av. Séneca 2, 28014 Madrid, Spain.*  
e-mail: rcalfer@bio.ucm.es

## **NASLIJEDE PO MAJČINOJ LINIJI U JUŽNOJ IBERIJI OTKRIVA DUBINE GENETSKE VEZE IZMEĐU KONTINENATA**

### **SAŽETAK**

U mediteranskom bazenu, Iberijski poluotok je u središtu atrakcija za nekoliko kultura i civilizacija iz svoje pretpovijesti i povijesti, što ga čini metom za proučavanje uzorka ljudskih migracija i koristeći široki i heterogeni spektar genetskih markera. Dok njegov Cantabrijski rub predstavlja najviše redovito analizirano područje u smislu njegove mitohondrijske raznolikosti, nepostojanje monografskih anketa o majčinskom genetskom sastavu južnih Ibera (tj. Andaluzana) je upečatljivo. U ovom radu predstaviti ćemo sveobuhvatan pogled na različite aspekte ljudskog majčinskog baštine autohtonog andaluzijskog stanovništva u pogledu specifičnih mitohondrijskih haplogrupa kao ključnim kandidatima za određivanje genetske veze između Europe i Afrike. Podaci pokazuju da je južne iberijske populacije nemaju genetski homogene mitohondrijske DNK profila, a njihov primijetna genetska sklonost sjeverozapadnim afričkim populacijama predstavlja jake signale starih te stalno I dvosmjerno ljudskih kretanje između sjeverne i južne obale zapadnog

Mediterrana. Temeljita analiza mtDNA afričke haplogrupe pokazala su da se najvažniji afrički doprinos iberijskom poluotoku može objasniti kao posljedica pretpovijesnih zbivanja. Kasnije povijesne epizode su pomogle jačanju veza između obje obale. U južnoj Iberiji, mitohondriji i drugi genetički markeri pokazuju da Gibraltarski tjesnac zajedno sa svojim okolnim morskim područjima treba uzeti u obzir kao most između kontinenata. U širem smislu, Sredozemno more je djelovalo kao transportna površina, ali i barijeru za ljudska migracija iz prapovijesnih i povijesnih vremena. Na kraju ovo istraživanje pridonosi našem znanju o procesima koji su oblikovali nedavnu ljudsku genetsku povijest u Sredozemlju, točnije, dinamike populacije koje su stanovnici južne Iberije doživjeli u odnosu na druge susjedne sjevernoafričkih populacija.