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ORIGINAL ARTICLE

An mtDNA perspective of French genetic variation

CHRYSTELLE RICHARD[1]*†, ERWAN PENNARUN[1,2]*, TOOMAS KIVISILD[2], KRISTIINA TAMBETS[2], HELLE-VIIVI TOLK[2], ENE METSPALU[2], MAERE REIDLA[2], SYLVIANA CHEVALIER[1], STÉPHANIE GIRAUDET[1], LOVORKA BARAĆ LAUC[2,3], MARIJANA PERIČIĆ[2,3], PAVAO RUDAN[3], MIREILLE CLAUSTRES[4], HUBERT JOURNEL[5], IAN DORVAL[6], CLAUDE MÜLLER[7], RICHARD VILLEMS[2], ANDRÉ CHAVENTRÉ[1], & JEAN-PAUL MOISAN[1]

[1]*Laboratoire d'Etude du Polymorphisme de l'ADN, Faculté de Médecine, Nantes, France,* [2]*Department of Evolutionary Biology, Institute of Molecular and Cell Biology, University of Tartu and Estonian Biocentre, Tartu, Estonia,* [3]*Institute for Anthropological Research, Zagreb, Croatia,* [4]*Laboratoire de Génétique Moléculaire, Institut Universitaire de Recherche Clinique IURC et CHU, Montpellier, France,* [5]*Unité de Génétique Médicale, CHR, Vannes, France,* [6]*Laboratoire de Biochimie-Biologie Moléculaire, Centre Hospitalier de Cornouaille, Quimper, France, and* [7]*Université Michel de Montagne-Bordeaux 3 & UMR 5610 CNRS, Synthaxe et Sémantique, Pessac, France*

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Abstract

Background: The French has been insufficiently characterized so far for mitochondrial DNA (mtDNA) diversity.

Aims: The study aimed to enhance the information available for the French mtDNA pool and to explore the potential microgeographical differentiation of two French regions selected for their linguistic and historical idiosyncrasies.

Subjects and methods: A total of 868 samples from 12 different locations in France were collected. They were sequenced for the hypervariable segment I (HVS-I) and typed for haplogroup defining markers from the coding region either by restriction fragment length polymorphism (RFLP) or by a new protocol based on the 5′ nuclease allelic discrimination. The mtDNA gene pools of French Basques and Bretons were compared in terms of frequency and composition with relevant neighbouring populations.

Results: The French Basques' mtDNA pool shares some common features with that of the Spanish Basques, such as the high frequency of haplogroup H. However, the French Basques exhibit a number of distinct features, most notably expressed in the prevalence of haplogroups linked with the

Correspondence: Erwan Pennarun, Department of Evolutionary Biology, Institute of Molecular and Cell Biology, University of Tartu and Estonian Biocentre, Riia 23, Tartu, 51010, Tartu, Estonia. E-mail: erwan@ebc.ee

*C.R. and E.P. contributed equally to this work.

†Present address: Institut de Génétique Nantes Atlantique, Nantes, France.

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Neolithic diffusion in Europe. In Brittany, Finistère shows closer affinities with Britain and Scandinavia than the two other departments of Brittany.
Conclusion: The mtDNA haplogroup composition of the French does not differ significantly from the surrounding European genetic landscape. At a finer grain, microgeographical differentiation can be revealed, as shown for the French Basque country and for Brittany.

Keywords: *Human mitochondrial DNA, France, microgeographical differentiation, phylogeography, Basque, Breton*

Introduction

The history of the settlement of France is a complex result of multiple migrations since the colonization of Europe by anatomically modern humans (AMH) in Palaeolithic times. The first AMH settled in France as early as 36 000 years ago, testified by the findings of numerous archaeological remains in southwestern France. These are generally linked to the Aurignacian culture, which is thought to have spread all over Europe from West Asia, with the earliest archaeological evidence slightly older than 40 000 years ago in Lower Danube (Bar-Yosef 1992; Mellars 2006). The Aurignacian was followed by other industries, among which the Gravettian culture covered almost all Europe from the Atlantic to the Urals from 29 000–22 000 years ago. Then around 20 000 years ago, the Last Glacial Maximum caused the depopulation of the septentrional and central zones of Europe, a time when the Solutrean culture developed in southern France and northern Spain. Around 15 000 years ago, the Magdalenian industry originated in Franco-Cantabria and is regarded as a signal of postglacial re-colonization from the southwestern part of Europe (Torroni et al. 2001; Achilli et al. 2004). The development and diffusion of agriculture was introduced in France by two main routes of Neolithization, one through central Europe to eastern France (Linearbandkeramik culture) and another from Dalmatia and Italy reaching the French Mediterranean coastline (Impressed-Cardial Ware culture) and yet another penetrating the Atlantic coast of France (Megalithic culture).

In the context of population genetics, the French have been examined mainly for HLA genes and protein polymorphisms (Comas et al. 1998; Gibert et al. 2000), as well as using haploid markers such as maternally inherited mitochondrial DNA (mtDNA) variation. We have studied 868 French mtDNA samples in order to substantially increase the so far existing data, with an emphasis on the French Atlantic fringe. We have also focused on two particular regions of France, because of their linguistic distinctiveness and past history. Brittany, which has been partially examined by others, has seen several important migrations coming across the channel (Boutouiller et al. 1997), and its native language belongs to Celtic. The French Basques are of particular interest because, so far, only the variation with the Spanish Basque mtDNA pool has been described (Bertranpetit et al. 1995; Corte-Real et al. 1996; Richards et al. 2000).

Materials and methods

DNA samples

A total of 788 DNA samples were obtained from healthy and unrelated French individuals, originating from 12 specified locations (nos 1–12 in Figure 1) and 80 from unspecified location in France. We have included in our analysis French data published by others

Figure 1. Geographic location of the analysed French samples by former region, with department of origin when available: Picardy (1, Somme $n=79$); Brittany (2, Finistère $n=120+22$ (Dubut et al. 2004); 3, Morbihan $n=41+40$ (Dubut et al. 2004); 4, Loire-Atlantique $n=75$; Maine-Anjou (5, Maine-et-Loire $n=55$; 6, Sarthe $n=36$); Poitou (7, Vendée $n=80$; 10, Vienne $n=44$); Béarn (8, Pyrénnées-Atlantiques $n=81$), Normandy (9, Calvados $n=46$; 13, Seine-Maritime $n=39$ (Dubut et al. 2004)); Languedoc (11, Hérault $n=85$); Lyonnais (12, Rhône $n=46$); Périgord-Limousin (14, $n=72$ (Dubut et al. 2004)); Provence (15, Var $=37$ (Dubut et al. 2004)); Corsica (16, $n=45$ (Varesi et al. 2000)) and North-East (17, $n=47$ (Richards et al. 2000)).

(Rousselet and Mangin 1998; Danan et al. 1999; Richards et al. 2000; Varesi et al. 2000; Cali et al. 2001). For a larger part of them, precise geographic origin has been reported (nos 13–17 in Figure 1), while 215 samples should be considered as 'general French', helpful only for a more robust inter-population comparison within Europe.

Because the current French departments are administrative territorial units established only 'recently' in 1790, long after most of the major waves of migrations, we analysed our samples on the basis of the historic French provinces (see Figure 1 for details). The comparative data set consisted of 11 210 mtDNA hypervariable segment I (HVS-I) sequences from different European populations (see Table SI, supplementary material; for details, see Appendix). Total DNA was extracted from whole blood by use of the Nucleon BACC2 extraction kit (Amersham Pharmacia®) or by the phenol–chloroform method, as used by Sambrook et al. (1989).

mtDNA amplification and sequencing

mtDNA HVS-I of the control region was amplified between nucleotide positions (nps) 15 970 and 16 420 of the revised Cambridge Reference Sequence (rCRS) (Andrews et al. 1999). Direct sequencing was performed and run in ABI PRISM® 3100 Genetic Analyzer (Applied Biosystems®). All sequences were read between nps 16 024 and 16 391 and aligned using the Genetics Computer Group (GCG) Wisconsin Package 10.0 (Womble 2000).

Analysis of coding region

mtDNA nucleotide substitutions in the coding region has been checked for 301 samples by restriction fragment length polymorphism (RFLP) analysis following published criteria (Torroni et al. 1996; Richards et al. 1998; Herrnstadt et al. 2002; Kivisild et al. 2002). For the other 567 samples, we have set up a new protocol based on the TaqMan® or 5′ nuclease allelic discrimination assay (Livak et al. 1995). For each assay, a fluorogenic oligonucleotide probe labelled with VIC was designed to anneal specifically to the rCRS allele, while a second probe labelled with 6-FAM was designed to anneal to the variant allele. This technique is faster than RFLP analysis and allowed a high throughput of the samples. All the sequences and coding region polymorphisms tested are reported in Table SII, supplementary material.

The primers and the MGB-Taqman® probes were synthesized by the manufacturer (Applied Biosystems®) and are reported in Table SIII, supplementary material. The PCR products were then analysed on an ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems®).

Statistical analysis

Principal component analyses (PCA) were performed as published earlier (Richards et al. 2002) using the software POPSTR, kindly provided by H. Harpending. The mtDNA data of some European populations were pooled into broader regional group as in the study by Richards et al. (2002) (see Table SI, supplementary material) in order to increase the total variation covered by the two first principal components.

Phylogenetic analysis

Haplogroups (Hgs) were assigned on the basis of both the HVS-I motifs and the coding region polymorphisms by use of published criteria (Torroni et al. 1996; Richards et al. 1998; Herrnstadt et al. 2002; Kivisild et al. 2002). Networks were constructed using the software Network 4.0.0.0 (Bandelt et al. 2000). Different weights were given to substitutions, as shown in the study by Richards et al. (1998).

Results

France, with its more than 60 millions of inhabitants and complex demographic history since the Palaeolithic, deserves a comprehensive survey of its mtDNA pool, based on balanced sampling all over the territory. Although not fully achieved (see Figure 1), we may nevertheless conclude, based on our summary results (Table SI, supplementary material), that the pattern of French mtDNA variation, as far as classical haplogroup frequencies are concerned, does not substantially differ from that one observes in its neighbouring countries, nor in Europe in general (some obvious outliers, detected already by classical markers (Cavalli-Sforza et al. 1994) notwithstanding, see Figure S1, supplementary material). Although this result is not unexpected, it is a needed step to fill an essential gap in the phylogeographic landscape of the European mtDNA variation. Within France itself, some outliers are also apparent, as shown on the PCA plot (Figure 2a), such as the Basques (from former region of Béarn) and the region of Provence, although the latter is more likely due to a small sample size (37 samples). Based on this and, as previously

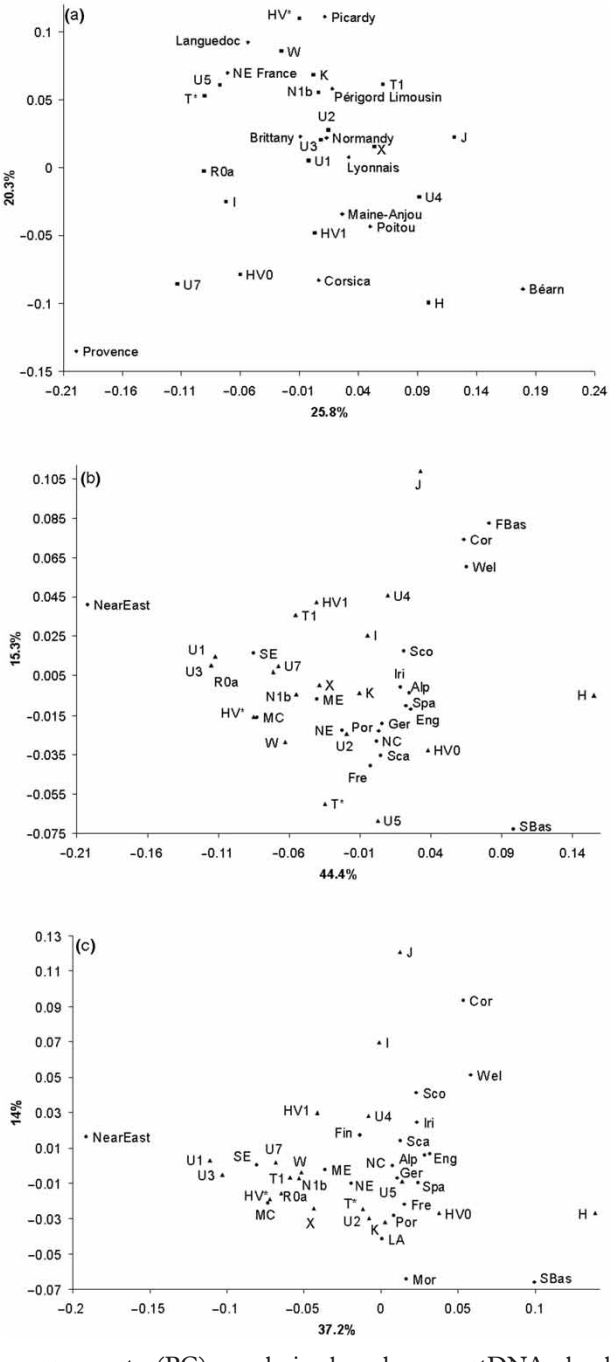

Figure 2. Principal component (PC) analysis based on mtDNA haplogroup frequencies. Abbreviations used are: Sca, Scandinavia; NE, North-East Europe; NC, North-Central Europe; Alp, Alpine; MC, Mediterranean Central; ME, Mediterranean East; SE, South-East Europe; Cor, Cornish; Eng, English; Fre, French (excluding French Basques in (a) and Bretons in (b)); Ger, Germans; Iri, Irish; Por, Portuguese; Sco, Scottish; Spa, Spanish; Wel, Welsh; Fin, Finistère; Mor, Morbihan; LA, Loire-Atlantique; FBas, French Basque; SBas, Spanish Basque. Circles represent populations and triangles haplogroups. (a) Historic French regions alone, (b) French Basques *vs*. Europeans, (c) Bretons *vs*. Europeans.

mentioned, a number of provinces of the country are of particular interest, based on their specific ethnic and linguistic history, and below we concentrate on their particularities.

The French Basques

Figure 2(b) shows principal component (PC) analysis of West Eurasian specific mtDNA haplogroups in Europe. On the first component, the Spanish and French Basques are driven to the same pole by their high frequency of Hg H. The second component, however, separates the French and Spanish Basques from each other. This component is mainly influenced by the opposing frequencies of Hg U4, frequent among the French Basques, and conversely U5, frequent in Spanish Basques (Table I). This difference is highlighted also on the median-joining network (Figure 3). It is somewhat surprising to find Hg U4 at a relatively high frequency (6.2%) and diversity among the French Basques (absent in Spanish Basques), because this sub-clade of U is largely East European and West Siberian (Tambets et al. 2003) in its distribution. In contrast to U4, Hg U5b2 is rare among French Basques (2.5%), and more frequent in the Spanish Basques. One other particularity of the French Basque is found within Hg J, more frequent than in the Spanish Basques (see Table I), and also the presence of the Hg J1c haplotype with HVS-I motif 16069-16126-16300. The derivatives of this branch of Hg J have been so far found mostly in Near Eastern populations (Richards et al. 2002; Metspalu et al. 2004; and authors' unpublished data). Likewise to U4, Hg T1 is found only in French Basques. This is particularly interesting when correlated with Hg J distribution, suggesting that mtDNA branches supposedly linked with Neolithic in the European context (Richards et al. 2000) are more frequent among the French Basques.

Bretons

Figure 2(c) shows PC analysis of the Breton mtDNA variation in the European context. In the first component, all samples cluster tightly together, while the second component

Table I. Excerpt from Table SI, displaying the frequencies of several haplogroups of relevance for Scandinavia, France, Spanish Basque country, the UK and Ireland. See Table SI for full details and references.

	n	H	HV0	I	J	K	T1	U4	U5
Scandinavia	2203	43.26%	4.13%	3.31%	10.12%	5.17%	1.13%	2.54%	13.66%
Norway	639	46.95%	4.07%	2.03%	10.02%	5.48%	0.94%	2.66%	11.58%
Finland	613	40.46%	6.53%	4.08%	5.55%	3.10%	1.14%	0.98%	22.19%
Sweden	503	42.94%	3.58%	2.39%	12.13%	5.57%	1.99%	4.57%	11.33%
Iceland	448	42.19%	1.56%	5.13%	14.29%	7.14%	0.45%	2.23%	7.59%
France	1385	45.56%	4.77%	2.02%	7.65%	8.74%	1.66%	2.31%	8.30%
Basque Country (Pyrénnées-Atlantiques)	81	58.02%	4.94%	–	17.28%	3.70%	3.70%	6.17%	2.47%
Brittany (Loire-Atlantique)	75	53.33%	4.00%	2.67%	2.67%	5.33%	1.33%	4.00%	6.67%
Brittany (Finistère)	142	35.00%	6.67%	4.17%	9.17%	8.33%	0.83%	1.67%	15.00%
Brittany (Morbihan)	81	44.44%	4.29%	–	6.17%	17.28%	4.94%	1.23%	6.17%
Basque Country (Spain)	156	58.97%	10.90%	–	2.56%	4.49%	–	–	12.18%
Scotland	891	45.12%	4.04%	4.38%	14.48%	6.73%	2.24%	2.47%	7.30%
Ireland	300	44.33%	5.67%	3.00%	10.67%	12.00%	1.33%	1.33%	8.33%
England	242	48.76%	3.72%	2.48%	11.98%	7.02%	2.07%	0.83%	8.68%
Cornwall	92	50.00%	2.17%	4.35%	19.57%	4.35%	2.17%	5.43%	6.52%
Wales	92	57.61%	4.35%	3.26%	15.22%	7.61%	2.17%	–	4.35%

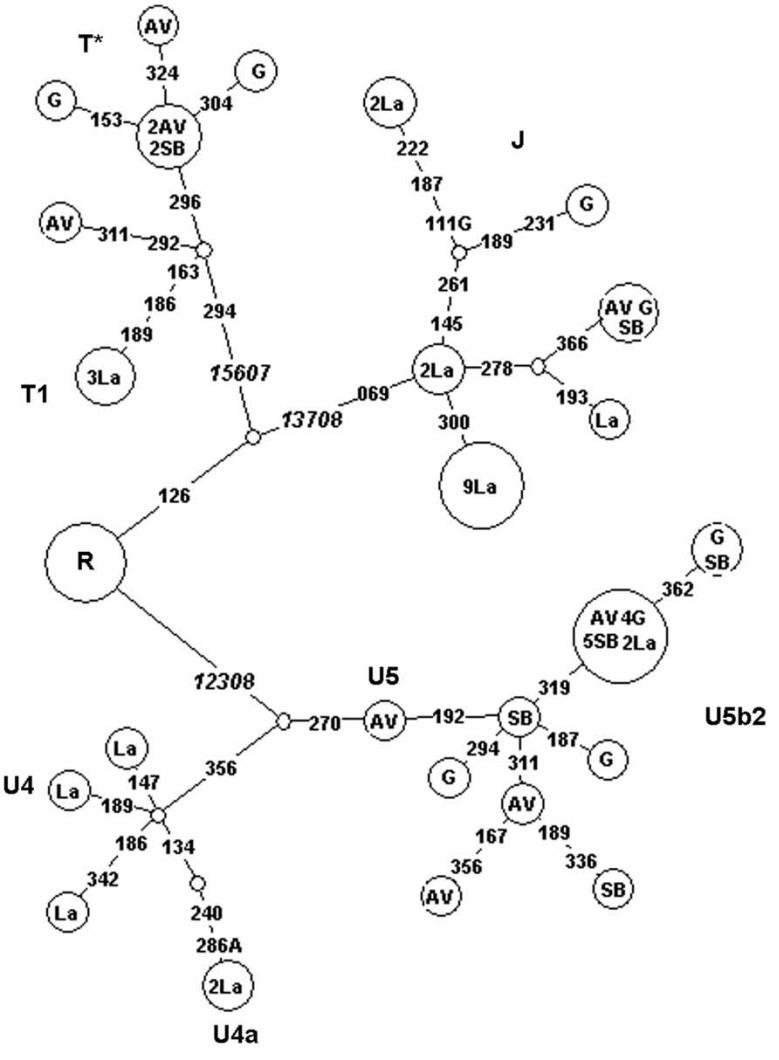

Figure 3. Median-joining network of haplogroups T, J, U4 and U5 from the Lapurdi population (present study, $n = 81$) and in the Spanish Basque population, including Alava and Viscaya sub-populations ($n = 61$ (Corte-Real et al. 1996)), Guipuzcoa sub-populations ($n = 45$ (Bertranpetit et al. 1995)) and 'general' Spanish Basques ($n = 50$ (Richards et al. 2000)). All mutations and nucleotide position numbers are given in respect to the revised Cambridge Reference Sequence (rCRS) (Andrews et al. 1999). Mutations are transitions; transversions are noted by a suffix. HVS-I variation is noted minus 16 000 while variation in the coding region is shown in italics. The sample code is as follows: La, Lapurdi; AV, Alava/Viscaya; G, Guipuzcoa; SB, Spanish Basques. The number of individuals when greater than 1 is written in the circle.

appears to be more informative. There, Finistère is closer to other Celtic-speaking populations (Irish, Scots, then Welsh and Cornish) than the two other departments in Brittany, because in Finistère, Hgs J and I are more frequent, while K and U2 are less frequent than in Morbihan and Loire-Atlantique.

Several other haplogroups are also of particular interest (see Figure 4). Firstly, Hg U5 is particularly frequent in Finistère, and one of its sub-clade characterized with mutation at

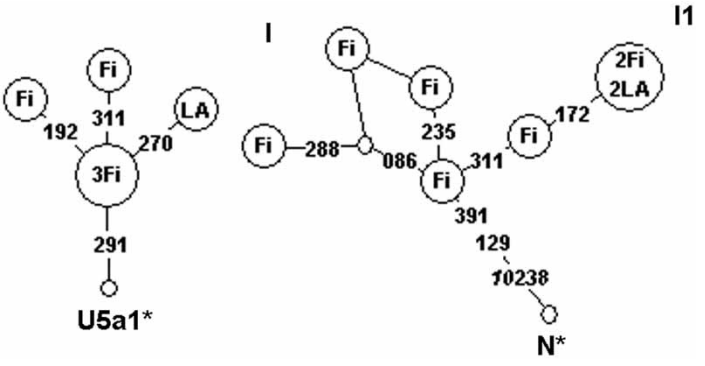

Figure 4. Median-joining network of haplogroups U5a with mutation at position 16 291 and I from Brittany. All mutations and nucleotide position numbers are given in respect to the revised Cambridge Reference Sequence (rCRS) (Andrews et al. 1999). Mutations are transitions; transversions are noted by a suffix. HVS-I variation is noted minus 16 000, while variation in the coding region is shown in italics. The sample code is as follows: Fi, Finistère; LA, Loire-Atlantique. The number of individuals when greater than 1 is written in the circle.

position 16291 is almost restricted to this area. This type represents in Finistère nearly a half of its total variety in France in samples covered so far. Elsewhere, perhaps importantly, it reaches its highest diversity and frequency in Scandinavia (1.3%). Similarly, haplogroup I, with the exception of one haplotype matching the nodal position of Hg I1, which we found in Loire-Atlantique (Table SII, supplementary material), is present only in Finistère. With a frequency of 5.0%, it is close to the frequency of haplogroup I in nearby Cornwall and in Iceland and Finland (Table I and Table SI, supplementary material). While haplogroup frequencies offer only general comparisons, the closer affinities between mtDNA pools of northwest France and the British Isles is supported also by a common Hg I HVS-I haplotype motif 16129-16223-16235-16 391 that seems to be restricted only to these regions.

Discussion

The French mtDNA pool has been largely unexplored until recently, leaving a considerable gap in the understanding of the phylogeography of the spread of maternal lineages in the part of Europe extending from the Mediterranean to the southern edge of the North Sea. The present study of 868 French mtDNA lineages significantly increases the sampling coverage of the region, yet must be considered as only the beginning of a more comprehensive mapping of the French mtDNA pool.

The Basque population is generally considered as a genetic outlier in Europe (Cavalli-Sforza et al. 1994). Whereas most of the genetic studies published on the variation of the modern and prehistoric Basques' mtDNA pools have been carried out in the Spanish side of Basque population (Bertranpetit et al. 1995; Corte-Real et al. 1996; Torroni et al. 1998; Izagirre and de la Rua 1999), we provide here the first data on the Basques from the Basque province of Lapurdi in France. Despite belonging to the Basque country, the mtDNA pattern of French Basques from the Lapurdi region was found to be quite different from that of Spanish Basques. The French Basques show a representative frequency of Hgs T1 and J that have been suggested to have been introduced to Europe with the advent

of Neolithization (Richards et al. 2000), being at the same time rare or absent among the Spanish Basques. On the other hand, haplogroups such as U5 and HV0 that are frequent in Spanish Basques are absent or rare in the French Basques, while for Hg U4 its distribution is the opposite. The pattern observed in the mtDNA pool of the French Basques from the Lapurdi region may be explained by genetic drift and cultural isolation in a relatively small long-term effective population size. In addition, it is also likely that both French and Spanish Basques, although sharing a common linguistic and probably also genetic ancestry, have been affected by admixture from different sources. Meanwhile, the overall high frequency of autosomal recessive coagulation factors deficiencies in French Basques population (Bauduer et al. 2004) argues in favour of genetic drift acting on this population. The cultural factor could have contributed to the maintenance of differences within small populations units, where territories are organized on the basis of villages, localized in valleys ('mountain cultures'). Taken together, our findings support the notion that 'Basques' are a strongly sub-divided population and support a conclusion that French and Spanish Basques have been effectively isolated from each other for a long enough period to allow random genetic drift to differentiate them. More importantly, our study shows that maternal lineages present in Basques cannot be treated as a representative set of the Palaeolithic mtDNA pool of Europeans (Dupanloup et al. 2004) as the presence of Hgs T1 and J revealed a possible Neolithic contribution. Rather, it is a mosaic of focal highs and lows, generated by gene flows and random drift in semi-isolated populations.

Brittany has seen several waves of migrations, some major ones coming mostly from the British Isles (Monnier and Jj 1997). Breton belongs to the same Brythonic branch of the Insular Celtic languages as Welsh (Forster and Toth 2003). Beside this obvious linguistic link, some genetic similarities are also apparent. mtDNA Hg I, which is well represented in Finistère, has a frequency close to that of Hg I found in the British Isles (Table I). Analogous resemblance has been described for the distribution of the mutations of cystic fibrosis (CF): mutation G551D is the second most frequent mutation for CF in both areas and is considered as a mutation that arose in the British Isles (Cashman et al. 1995). The high genetic heterogeneity, still observable between different regions of Brittany, is interesting, and can be, at least in part, explained by the influence of the historic gene flows that involved different tribes coming from different areas of the British Islands. Each tribe settled down to a specific part of Brittany as illustrated by the names of different regions, which are common on both sides of the Channel (e.g. Cornouailles–Kerne in Breton and Cornwall–Kernow in Cornish). Some shared features of Bretons, especially in Finistère, with northern European regions reveal genetic influences of other migrations. For instance, the mtDNA sub-clade of U5a characterized with mutation at position 16291 that is notably frequent in Scandinavia is particularly present in Finistère. This points to the possibility that the gene flow from Scandinavia that in its major part probably took place during the Viking invasions in the 9th century was indeed intensive, even though some historians believe that the Norse expansion has mainly implicated males (Clover 1986). Another hypothesis could be that Bretons and Scandinavians have some common features dating back to the re-population of Scandinavia after the Last Glacial Maximum. A similar geographic pattern has been also revealed by the analysis of the polymorphisms of the chemokine receptor CCR5 gene (Libert et al. 1998).

Summing up, one may conclude that in most general terms, the mtDNA pool of the French population fits well to the surrounding genetic landscape of Western Europe. However, when the French historic regions are considered, substantial differences at the

microgeographic level can be revealed, as was shown here using the example of the Basques and Bretons—two obvious choices from a historic, as well as linguistic, point of view.

It appears that the total French mtDNA database, at a median level of resolution such as provided here, can be considered as already large in the so-far published European mtDNA variation. Yet a glance at Figure 1 shows that considerable further efforts are required to achieve more representative coverage of the whole country. There are at least two important reasons why this is advisable. First, for better understanding of the genetic history of European populations, where France, in particular its south-western provinces, may have had a special role during the re-peopling of Europe after the Last Glacial Maximum (Torroni et al. 2001; Achilli et al. 2004). Secondly, it is increasingly obvious that deeper understanding of the emergence of natural genetic variation enhances the possibilities to explore disease associations.

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Appendix: Supplementary material

Supplementary Figure S1 and Tables SI, SII and SIII are available at the web site of the Department of Evolutionary Biology: http://evolutsioon.ut.ee/Supplementary.html

Figure SI. Principal component (PC) analysis based on mtDNA haplogroup frequencies. Abbreviations used are: Sca, Scandinavia; NE, North-East Europe; NC, North-Central Europe; Alp, Alpine; MC, Mediterranean Central; ME, Mediterranean East; SE, South-East Europe; Cor, Cornish; Eng, English; Fre, French; Ger, Germans; Iri, Irish; Por, Portuguese; Sco, Scottish; Spa, Spanish; Wel, Welsh; SBas, Spanish Basque. Circles represent populations and triangles haplogroups.

Table SI. mtDNA haplogroups frequency in various European populations and Turks.

Table SII. HVS-I sequence between positions 16 024 and 16 391 (minus 16 000) according to the rCRS with relevant coding region information in 868 French samples.

Table SIII. List of polymorphisms tested for each haplogroup and probes and primers used for TaqMan® assay.

References

Achilli A, Rengo C, Magri C, Battaglia V, Olivieri A, Scozzari R, Cruciani F, Zeviani M, Briem E, Carelli V, et al. 2004. The molecular dissection of mtDNA haplogroup H confirms that the Franco-Cantabrian glacial refuge was a major source for the European gene pool. Am J Hum Genet 75:910–918.

Andrews RM, Kubacka I, Chinnery PF, Lightowlers RN, Turnbull DM, Howell N. 1999. Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA. Nat Genet 23:147.

Bandelt H-J, Macaulay V, Richards M. 2000. Median networks: Speedy construction and greedy reduction, one simulation, and two case studies from human mtDNA. Mol Phylogenet Evol 16:8–28.

Bar-Yosef O. 1992. The role of western Asia in modern human origins. Philos Trans R Soc Lond B Biol Sci 337:193–200.

Bauduer F, Ducout L, Dutour O, Degioanni A. 2004. Is there a 'Basque' profile regarding autosomal recessive deficiencies of coagulation factors? Haemophilia 10:276–279.

Bertranpetit J, Sala J, Calafell F, Underhill PA, Moral P, Comas D. 1995. Human mitochondrial DNA variation and the origin of Basques. Ann Hum Genet 59:63–81.

Boutouiller P, Briard J, Brunel C, Canevet C, Carney S, Cassard JJ, Castel YP, Galliou P, Geslin C, Grall P, et al. 1997. Toote L'histoire de Bretagne. Morlaix: Skol Vreizh.

Cali F, Le Roux MG, D'Anna R, Flugy A, De Leo G, Chiavetta V, Ayala GF, Romano V. 2001. MtDNA control region and RFLP data for Sicily and France. Int J Legal Med 114:229–231.

Cashman SM, Patino A, Martinez A, Garcia-Delgado M, Miedzybrodzka Z, Schwarz M, Shrimpton A, Ferec C, Raguenes O, Macek Jr M, et al. 1995. Identical intragenic microsatellite haplotype found in cystic fibrosis chromosomes bearing mutation G551D in Irish, English, Scottish, Breton and Czech patients. Hum Hered 45:6–12.

Cavalli-Sforza LL, Menozzi P, Piazza A. 1994. The history and geography of human genes. Princeton: Princeton University Press.

Clover C. 1986. Maiden warriors and other sons. J English Germanic Philology 85:35–49.

Comas D, Calafell F, Mateu E, Perez-Lezaun A, Bertranpetit J. 1998. HLA evidence for the lack of genetic heterogeneity in Basques. Ann Hum Genet 62:123–132.

Corte-Real HB, Macaulay VA, Richards MB, Hariti G, Issad MS, Cambon-Thomsen A, Papiha S, Bertranpetit J, Sykes BC. 1996. Genetic diversity in the Iberian Peninsula determined from mitochondrial sequence analysis. Ann Hum Genet 60:331–350.

Danan C, Sternberg D, Van Steirteghem A, Cazeneuve C, Duquesnoy P, Besmond C, Goossens M, Lissens W, Amselem S. 1999. Evaluation of parental mitochondrial inheritance in neonates born after intracytoplasmic sperm injection. Am J Hum Genet 65:463–473.

Dubut V, Chollet L, Murail P, Cartault F, Beraud-Colomb E, Serre M, Mogentale-Profizi N. 2004. mtDNA polymorphisms in five French groups: Importance of regional sampling. Eur J Hum Genet 24:293–300.

Dupanloup I, Bertorelle G, Chikhi L, Barbujani G. 2004. Estimating the impact of prehistoric admixture on the genome of europeans. Mol Biol Evol 21:1361–1372.

Forster P, Toth A. 2003. Toward a phylogenetic chronology of ancient Gaulish, Celtic, and Indo-European. Proc Natl Acad Sci USA 100:9079–9084.

Gibert M, Reviron D, Mercier P, Chiaroni J, Boetsch G. 2000. HLA-DRB1 and DQB1 polymorphisms in southern France and genetic relationships with other Mediterranean populations. Hum Immunol 61:930–936.

Herrnstadt C, Elson JL, Fahy E, Preston G, Turnbull DM, Anderson C, Ghosh SS, Olefsky JM, Beal MF, Davis RE, et al. 2002. Reduced-median-network analysis of complete mitochondrial DNA coding-region sequences for the major African, Asian, and European haplogroups. Am J Hum Genet 70:1152–1171.

Izagirre N, de la Rua C. 1999. An mtDNA analysis in ancient Basque populations: Implications for haplogroup V as a marker for a major Palaeolithic expansion from southwestern Europe. Am J Hum Genet 65:199–207.

Kivisild T, Tolk HV, Parik J, Wang Y, Papiha SS, Bandelt HJ, Villems R. 2002. The emerging limbs and twigs of the East Asian mtDNA tree. Mol Biol Evol 19:1737–1751.

Libert F, Cochaux P, Beckman G, Samson M, Aksenova M, Cao A, Czeizel A, Claustres M, De La Rua C, Ferrari M, et al. 1998. The deltaccr5 mutation conferring protection against HIV-1 in Caucasian populations has a single and recent origin in Northeastern Europe. Hum Mol Genet 7:399–406.

Livak KJ, Flood SJ, Marmaro J, Giusti W, Deetz K. 1995. Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization. PCR Methods Appl 4:357–362.

Mellars P. 2006. Going east: New genetic and archaeological perspectives on the modern human colonization of Eurasia. Science 313:796–800.

Metspalu M, Kivisild T, Metspalu E, Parik J, Hudjashov G, Kaldma K, Serk P, Karmin M, Behar DM, Gilbert MT, et al. 2004. Most of the extant mtDNA boundaries in south and southwest Asia were likely shaped during the initial settlement of Eurasia by anatomically modern humans. BMC Genet 5:26.

Richards M, Macaulay V, Hickey E, Vega E, Sykes B, Guida V, Rengo C, Sellitto D, Cruciani F, Kivisild T, et al. 2000. Tracing European founder lineages in the Near Eastern mtDNA pool. Am J Hum Genet 67:1251–1276.

Richards M, Macaulay V, Torroni A, Bandelt HJ. 2002. In search of geographical patterns in European mitochondrial DNA. Am J Hum Genet 71:1168–1174.

Richards MB, Macaulay VA, Bandelt HJ, Sykes BC. 1998. Phylogeography of mitochondrial DNA in western Europe. Ann Hum Genet 62:241–260.

Rousselet F, Mangin P. 1998. Mitochondrial DNA polymorphisms: A study of 50 French Caucasian individuals and application to forensic casework. Int J Legal Med 111:292–298.

Sambrook J, Fritsch EF, Maniatis T. 1989. Molecular cloning: A laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Tambets K, Tolk HV, Kivisild T, Metspalu E, Parik J, Reidla M, Voevoda M, Damba L, Bermisheva M, Khusnutdinova E, et al. 2003. Complex signals for population expansions in Europe and beyond. In: Bellwood P, Renfrew C, editors. Examining the farming/language dispersal hypothesis. Cambridge: McDonald Institute for Archaeological Research Monograph Series, Cambridge University.

Torroni A, Bandelt HJ, D'Urbano L, Lahermo P, Moral P, Sellitto D, Rengo C, Forster P, Savontaus ML, Bonne-Tamir B, et al. 1998. mtDNA analysis reveals a major late Paleolithic population expansion from southwestern to northeastern Europe. Am J Hum Genet 62:1137–1152.

Torroni A, Bandelt HJ, Macaulay V, Richards M, Cruciani F, Rengo C, Martinez-Cabrera V, Villems R, Kivisild T, Metspalu E, et al. 2001. A signal, from human mtDNA, of postglacial recolonization in Europe. Am J Hum Genet 69:844–852.

Torroni A, Huoponen K, Francalacci P, Petrozzi M, Morelli L, Scozzari R, Obinu D, Savontaus ML, Wallace DC. 1996. Classification of European mtDNAs from an analysis of three European populations. Genetics 144:1835–1850.

Varesi L, Memmi M, Cristofari MC, Mameli GE, Calo CM, Vona G. 2000. Mitochondrial control-region sequence variation in the Corsican population, France. Am J Human Biol 12:339–351.

Womble DD. 2000. GCG: The Wisconsin Package of sequence analysis programs. Methods Mol Biol 132:3–22.