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Major genomic mitochondrial lineages delineate early human expansions

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Abstract

Background: The phylogeographic distribution of human mitochondrial DNA variations allows a genetic approach to the study of modern *Homo sapiens* dispersals throughout the world from a female perspective. As a new contribution to this study we have phylogenetically analysed complete mitochondrial DNA(mtDNA) sequences from 42 human lineages, representing major clades with known geographic assignation.

Results: We show the relative relationships among the 42 lineages and present more accurate temporal calibrations than have been previously possible to give new perspectives as how modern humans spread in the Old World.

Conclusions: The first detectable expansion occurred around 59,000–69,000 years ago from Africa, independently colonizing western Asia and India and, following this southern route, swiftly reaching east Asia. Within Africa, this expansion did not replace but mixed with older lineages detectable today only in Africa. Around 39,000–52,000 years ago, the western Asian branch spread radially, bringing Caucasians to North Africa and Europe, also reaching India, and expanding to north and east Asia. More recent migrations have entangled but not completely erased these primitive footprints of modern human expansions.

Background

Human mtDNA is a non-recombining molecule with maternal inheritance and practically haploid genetics. Differences between mtDNA sequences are only due to mutation. As time passes, mutations accumulate sequentially along less and less related molecules that constitute independent lineages known as haplotypes. Relationships among lineages can be estimated by phylogenetic networks [1] where mutations are classified in hierarchical levels. Basal mutations are shared for clusters of lineages, defined as haplogroups, whereas those at the tips characterize individuals. Major haplogroups [2] are continental or ethnically specific. Three of them (L1, L2, and L3) group sub-Saharan African lineages, nine (H, I, J, K, T, U, V, W and X) encompass almost all mtDNAs from European, North African and Western Asian Caucasians. Finally, haplogroups A, B, C, D, E, F, G and M embrace the majority of the lineages described for Asia, Oceania and native Americans. The geographic distribution of derived branches of these haplogroups has shed light on

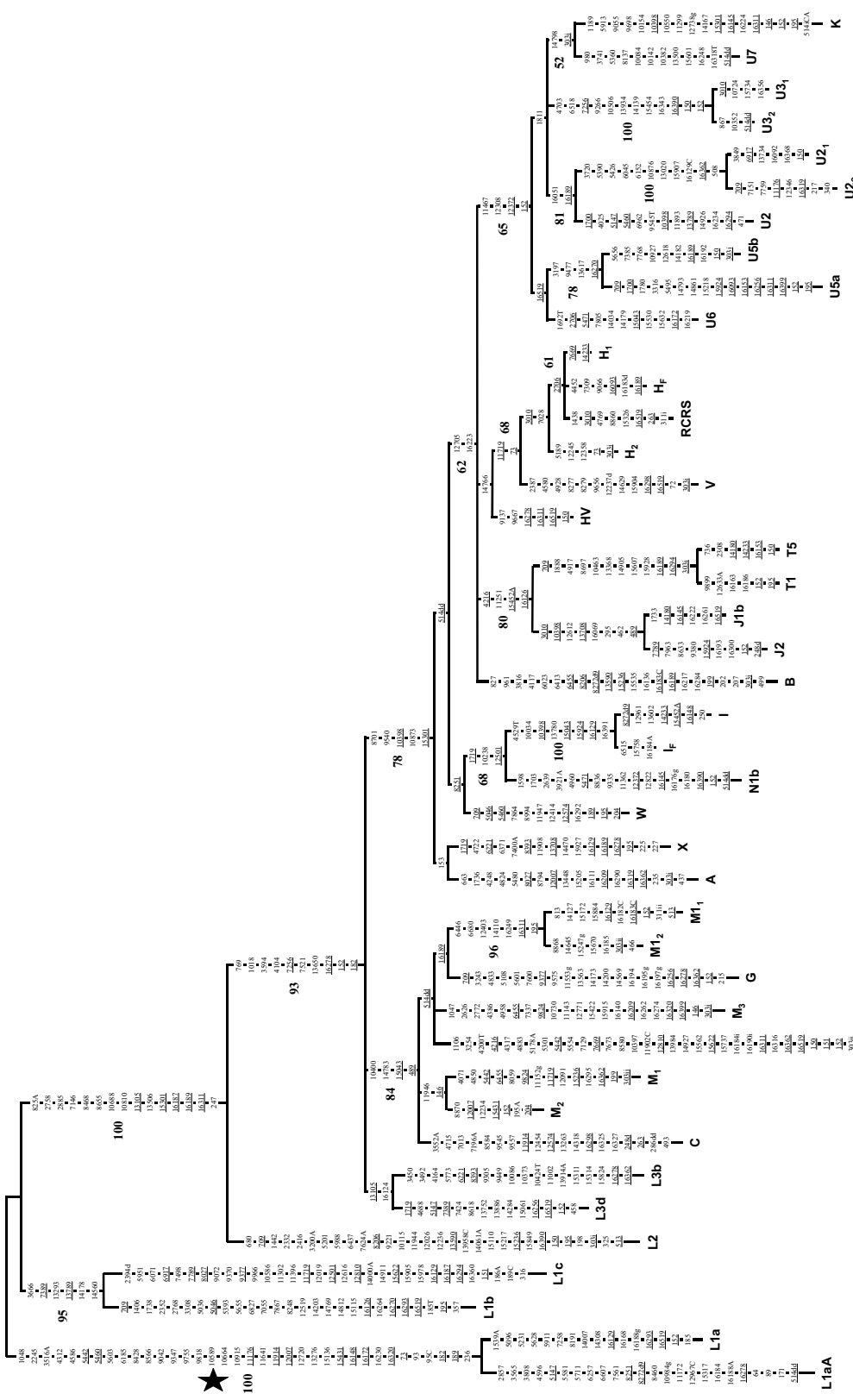

Figure 1
Phylogenetic network based on complete mtDNA genome sequences. Nomenclature of individuals is as in Table I. Numbers along the links refer to nucleotide positions; suffixes are transversions; underlining indicates recurrent mutations; the order of the mutations on a path not interrupted by any branching or distinguished nodes is arbitrary. The same topology was supported by bootstraps, using NJ and 1000 replicates; the bootstrap values higher than 50% are shown over the branches. The star shows the position where the chimpanzee sequence roots in the network.

crucial aspects of human history, such as the probable origin and approximate dating of migrations into the New World [3] and Polynesia [4,5], and quantitative estimations of the relative Paleolithic and Neolithic contributions to the extant European mtDNA diversity [2]. At the other end of the phylogenetic tree, the ultimate coalescence of all worldwide mtDNA lineages into Africa has favored, since the beginning, the recent African origin hypothesis for all modern humans [6]. The analyses of the complete mtDNA sequence of 53 humans of diverse origins [7] have added statistical support to this hypothesis. However, as the current definition of the major haplogroups is not based on total genomic sequences, there is not yet a clear resolution of their basal relationships. This genomic phylogenetic reconstruction is necessary to infer the early human dispersal routes after the African exodus. We present the phylogenetic network of 42 complete mtDNA sequences including representatives of the major haplogroups. Based on their relative clustering and coalescence ages we propose a tentative model of the way the Old World could have been colonized by modern humans.

Results and Discussion

The phylogenetic network of the 42 mtDNA sequences (Fig. 1) was free of reticulations when mutations [8] 150, 152, 303i and 16519 were omitted in its construction. The tree topology was the same as the bootstrap supporting neighbor joining tree. We detected 35 parallel substitutions from 124 variable positions (28%) in the non-coding region (1,122 bp in length), and 45 from 409 (11%) in the coding region (15,447 bp in length). Shared mutations in basal branches of the tree relate haplogroups, however, parallel mutations should be avoided in their global affiliations. As can be expected from haplotypes of well-differentiated haplogroups the majority of mutations are in the external branches of the tree, including those that specifically define them [2]. Nevertheless, it is well known that in population studies these main lineages sprout into several sub-clusters sometimes with interesting geographic localization. In the cases where representatives of these sub-clusters have also been analyzed, it is evident that the African ones are at the same level of divergence as non-African clusters. More information of cluster structure in Africa is necessary. In non African groups, two haplotypes belonging to sub-haplogroup U2 have a divergence similar to that found between other sub-clusters of the Caucasian U haplogroup. One of them, lacking mutations 16129C and 15907, that are present in all western Eurasian representatives, resembles haplotypes found in India [9]. The proposed inclusion of haplogroup K into the U cluster [10] is confirmed, being U7 its most probable related sub-clade. Main Asian haplogroups belong to two different major clusters, whereas A and B rooted with Caucasoid haplogroups, C, D, G and M constitute a monophyletic cluster. Likewise, African haplogroup L3 is more related to Eurasian haplogroups than to the most divergent African clusters L1 and L2. Chimpanzee rooting shows that the oldest lineage of extant modern humans is the African L1a cluster. In addition, the significant bootstrap values on the deep African branches reinforce the statistical support that the out of Africa hypothesis has obtained through a parallel genomic mtDNA study [7]. We have estimated a minimum total coalescence for modern human lineages from 156,000 to 169,000 years before present (yr BP). The two subsequent ancient splits also happened inside Africa, originating the L1b/c and L2 haplogroups with ages of 122,000–132,000 yr BP and 85,000–95,000 yr BP respectively. These three clades still have an overwhelming sub-Saharan African implantation. The next branching (Fig. 2), dated between 59,000–69,000 yr BP, also occurred in Africa but comprising clades currently found only in this continent (L3), and others with a first expansion out of Africa. Today, L3 derivatives are present in nearly all the African populations. This ancient spread inside Africa has been directly detected by the ages of several sub-clade expansions [11] and indirectly confirmed by genetic admixture, involving archaic and modern autosomal gene alleles, detected only in Africa [12]. The coexistence in African populations of very divergent non-recombining lineages may erroneously bias demographic estimations based on pair-wise nucleotide differences [11]. Two hypothetical routes for the Asian colonization have been proposed [13], one through Central Asia and one through South Asia. Coincidentally, we detect at least two independent lineages spreading out of Africa. One comprises all M de-

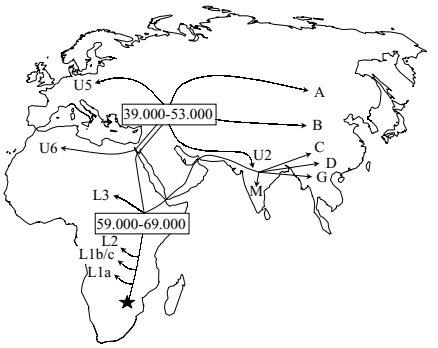

Figure 2
Geographic dispersal routes and minimal estimated ages of major human expansions in the Old World, deduced from the age and geographic localisation of main mtDNA haplogroups.

Table 1: HVS I motifs

Sample	HVS I motif	Haplogroup	Origin	Ref.[a]
K	145 224 311	K	Iberian	1
U7	248 318T	U7	Iberian	1
$U3_1$	343 356 390	U3	Canarian	1
$U3_2$	343 390	U3	Moroccan	1
$U2_1$	051 092 129C 189 362 368	U2	Jordanian	1
$U2_2$	051 129C 189 319 362	U2	Iberian	1
U2	051 189 234 294	U2	Jordanian	1
U5b	189 192 270	U5b	Berber	1
U5a	093 153 256 270 311 399	U5a1a	Swede	2
U6	172 219	U6	Moroccan	1
H_1		H	Mauritanian	1
H_F	093 183d 189	H		3
RCRS		H	European	4
H_2		H	Iberian	1
V	298	V	Berber	1
HV	278 311	HV	Jordanian	1
T5	126 153 189 294	T5	Moroccan	1
T1	126 163 186 189 294	T1	Iberian	1
J1b	069 126 145 222 261	J1b	Moroccan	1
J2	069 126 193 300	J2	Iberian	1
B	136 183C 189 217 284	B	Japanese	5
I	129 148 223 391	I	Iberian	1
I_F	129 184A 223 391	I		3
N1b	145 176G 180 223 390	N1b	Jordanian	1
W	223 292	W	Iberian	1
X	129 189 223 278	X	Moroccan	1
A	111 209 223 290 319 362	A	Canarian	1
$M1_1$	129 182C 183C 189 223 249 311	M1	Moroccan	1
M12	185 189 223 249 311	M1	Jordanian	1
G	189 194 195G 197G 223 256 278 362	G	Japanese	6
M_3	140 209 223 262 274 320 399	M	Japanese	7
D	184iC 190iC 223 311 316 362	D	Japanese	6
M_1	223 295 362	M	Filipino	1
M_2	223	M	Indian	1
C	223 298 325 327	C	Canarian	1
L3b	124 223 278 362	L3b	Mauritanian	1
L3d	124 223 256	L3d	Jordanian	1
L2	223 278 390	L2	Mauritanian	1
L1c	129 189 223 278 294 311 360	L1c	Mauritanian	1
L1b	126 187 189 223 264 270 278 293 311	L1b	Mauritanian	1
L1a	129 148 168 172 187 188G 189 223 230 278 293 311 320	L1a	Moroccan	1
L1aA	148 172 184 187 188A 189 223 230 311 320	L1a	African	8

[a] 1, This work; 2, GenBank accession number X93334; 3, H and I references [34], we have added for the comparisons the 263, 311i and 16519 mutations in both sequences and 00073 in the I sequence; 4, revised Cambridge reference, GenBank accession number NC 001807; 5, Positive control [35], for comparisons we added 1438; 6, MELAS, P-1 (G) and FICM (D) [36]; 7, (ref [37]); 8, GenBank accession number D38112, for comparisons we added 311i.

rivatives that radiated 30,000–57,600 yr BP. Subsequent expansions of this clade have been found in India [9] and Eastern Asia where it possibly originated and expanded as haplogroups C, D, G and others [14]. The star-like radiation of these clades suggests that this wide geographic colonization could have happened in a relatively short time. Genetic support for this southern spread of M through Ethiopia and the Arabian Peninsula along South

Asia has been recently proposed due to the presence of subclade M1 in Eastern Africa [15]. However, a posterior return from Asia to Africa of these lineages is a more plausible explanation because the genetic diversity of M is much greater in India [9] than in Ethiopia [15]. In fact, M1 could be a branch of the Indian cluster M as ancestral motifs of the African M1 are found in M*, M3 and M4 Indian subclusters [16]. Furthermore, one of the most derived M3 haplotypes in India (10398, 10400, 16086, 16129, 16223, 16249, 16259, 16311) has all the basic substitutions that defined the Ethiopian clade, excepting the highly variable 16189 [9]. This supposed Indian expansion to the west also reached northern areas since evolved representatives of M4 have been also detected in Central Asia [17]. We may consider the upper bound for this return to Africa 25,000–47,000 yr BP, the age calculated for M1 in Eastern Africa based on HVSI sequences or 33,000–63,000 obtained using RFLPs [15].

The other major branch that left Africa gave rise mainly to Caucasoid lineages which is congruent with a northern route through the Levant. With a lower bound of 43,000–53,000 yr BP this branch spread into at least three main clusters. One comprises haplogroups X and A with only a shared mutation between them and different geographic distributions. Whereas A is widespread in Asia, X is mainly restricted to Europe. Curiously, representatives of both clusters have been detected in native Americans raising the possibility that some American Indian could have European ancestry [18]. Nevertheless, X haplotypes have recently been detected in Central Asia. These Asian X haplotypes lack the 225A mutation, as the majority of the American X, pointing to this area as the most probable source for the dispersal of the New World founders [19]. The second cluster groups minor haplogroups W, I and N1b, the three are present although in low frequencies in Europe, Near East and Caucasus but only I and N1b have been also detected in Egypt and Arabia [2]. The last group radiated around 39,000–52,000 yr BP, giving at least four ancestral clusters. One of them originated haplogroup B that expanded to Eastern Asia, reaching Japan and southeastern Pacific Archipelagos [20,21]. In early studies, this clade was defined by the 9-bp COII-tRNA^{Lys} deletion but after that it has been found with independent origins on other haplogroup backgrounds [22–24]. In this study we have detected this deletion on an Iberian haplotype belonging to haplogroup I. Curiously, it was also found in an Italian haplotype I [25]. However, the 9-bp deletion was absent in a wide screen that we carried out on Iberian and Northwest African I haplotypes. The detection in two Mediterranean populations of I haplotypes harboring the 9-bp deletion points to the existence in this area of a subset of I haplotypes that share a recent common ancestor. As happens with A, haplogroup B has not been found in northern India [9] but is present in Mongolia [26], favoring a Central Asian route for the expansion of these prominent Asian haplogroups. Two additional clades join haplogroups J and T and haplogroups H, V and HV respectively. Derivatives of at least some of them are found in Europe, North Africa, Central Asia and even India, but the most probable origin for all these expansions is the Near East-Caucasus area [2,17,27]. Finally, cluster U seems to have suffered a radial spread (Fig. 2), giving subsequent diversification in different geographic areas. Three sub-haplogroups, U2, U5 and U6 had their major expansions in India, Europe and North Africa respectively. U2 split in two branches, one, characterized by mutations 16129C and 15907, is geographically scattered from Western Europe to Mongolia [2,26] but has not been detected in North Africa. The other reached India where it gave origin to several sub-clusters with global frequencies around 10% being, after its predecessor haplogroup M (53%), the second most abundant haplogroup in India [9]. U7 with a minor implantation in Europe but third in frequency in India [9] and also not detected in North Africa might have had a similar expansion as U2. The main radiation of haplogroup U5 occurred in Europe. It has been stated that this lineage entered Europe during the Upper Paleolithic [2], most probably from the Middle East-Caucasus area. The great divergence found here for the two U5 representatives is in agreement with the old age proposed for this haplogroup. Finally, U6 traces the first detectable Paleolithic return to Africa of ancient Caucasoid lineages. It has been mostly found in Northwest Africa, with a global estimated age of 47,000 years [28] reflecting an old human continuity in that rather isolated area. The fact that in Europe it has only been detected in the Iberian Peninsula [29] rules out a possible European route, unless a total lineage extinction in all the path is invoked. On the other hand, its presence in Northeast Africa [30], albeit in low frequencies, reinforces its way through North Africa. A third possibility could be that this lineage never went out of Africa but its coalescence with clades which all had prominent expansions in Eurasia weakens this option. U3 has also been found with a comparatively higher frequency in Northwest Africa [29] and might have followed the same route as U6, however, as its star-like expansion in the Caucasus has been dated around 30,000 yr BP [30], it most probably reached Africa in a posterior expansion. This out of Africa and back again hypothesis has also been suggested for Y-chromosome lineages [31]. Subsequent Neolithic and historic expansions have doubtlessly reshaped the human genetic pool in wide geographic areas but mainly as limited gene flow, not admixture, between populations. Consequently, the continental origin of the major haplogroups can still be detected and the earliest human routes inferred through them.

Table 2: Oligonucleotide pairs used in the amplification and sequencing

Name	CRS reference	Sequence (5'–3')	Fragment size (pb)	Annealing temp.(°C)
L16340	(16318–16340)	AGCCATTTACCGTACATAGCACA	681	52
H408	(429–408)	TGTTAAAAGTGCATACCGCCA		
L382	(362–382)	CAAAGAACCCTAACACCAGCC	603	56
H945	(964–945)	GGGAGGGGGTGATCTAAAAC		
L923	(902–923)	GTCACACGATTAACCCAAGTCA	607	56
H1487	(1508–1487)	GTATACTTGAGGAGGGTGACGG		
L1466	(1445–1466)	GAGTGCTTAGTTGAACAGGGCC	629	58
H2053	(2073–2053)	TTAGAGGGTTCTGTGGGCAAA		
L2025	(2004–2025)	GCCTGGTGATAGCTGGTTGTCC	609	52
H2591	(2612–2591)	GGAACAAGTGATTATGCTACCT		
L2559	(2538–2559)	CACCGCCTGCCCAGTGACACAT	591	56
H3108	(3128–3108)	TCGTACAGGGAGGAATTTGAA		
L3073	(3051–3073)	AAAGTCCTACGTGATCTGAGTTC	640	52
H3670	(3690–3670)	GGCGTAGTTTGAGTTTGATGC		
L3644	(3625–3644)	GCCACCTCTAGCCTAGCCGT	623	58
H4227	(4247–4227)	ATGCTGGAGATTGTAATGGGT		
L4210	(4189–4210)	CCACTCACCCTAGCATTACTTA	625	55
H4792	(4813–4792)	ACTCAGAAGTGAAAGGGGGCTA		
L4750	(4729–4750)	CCAATACTACCAATCAATACTC	599	52
H5306	(5327–5306)	GGTGATGGTGGCTATGATGGTG		
L5278	(5259–5278)	TGGGCCATTATCGAAGAATT	593	58
H5832	(5851–5832)	GACAGGGGTTAGGCCTCTTT		
L5781	(5762–5781)	AGCCCCGGCAGGTTTGAAGC	626	58
H6367	(6387–6367)	TGGCCCCTAAGATAGAGGAGA		
L6337	(6318–6337)	CCTGGAGCCTCCGTAGACCT	601	58
H6899	(6918–6899)	GCACTGCAGCAGATCATTTC		
L6869	(6850–6869)	CCGGCGTCAAAGTATTTAGC	578	58
H7406	(7427–7406)	GGGTTCTTCGAATGTGTGGTAG		
L7379	(7358–7379)	AGAAGAACCCTCCATAAACCTG	580	56
H7918	(7937–7918)	AGATTAGTCCGCCGTAGTCG		
L7882	(7861–7882)	TCCCTCCCTTACCATCAAATCA	506	56
H8345	(8366–8345)	TTTCACTGTAAAGAGGTGTTGG		
L8299	(8280–8299)	ACCCCCTCTAGAGCCCACTG	603	56
H8861	(8882–8861)	GAGCGAAAGCCTATAATCACTG		
L8799	(8779–8799)	CTCGGACTCCTGCCTCACTCA	638	58
H9397	(9416–9397)	GTGGCCTTGGTATGTGCTTT		
L9362	(9342–9362)	GGCCTACTAACCAACACACTA	609	56
H9928	(9950–9928)	AACCACATCTACAAAATGCCAGT		
L9886	(9865–9886)	TCCGCCAACTAATATTTCACTT	617	56
H10462	(10481–10462)	AATGAGGGGCATTTGGTAAA		
L10403	(10383–10403)	AAAGGATTAGACTGAACCGAA	612	56
H10975	(10994–10975)	CCATGATTGTGAGGGGTAGG		
L10949	(10930–10949)	CTCCGACCCCCTAACAACCC	617	58
H11527	(11546–11527	CAAGGAAGGGGTAGGCTATG		
L11486	(11467–11486	AAAACTAGGCGGCTATGGTA	629	56
H12076	(12095–12076	GGAGAATGGGGGATAGGTGT		
L12028	(12008–12028	GGCTCACTCACCCACCACATT	615	58
H12603	(12623–12603	ACGAACAATGCTACAGGGATG		
L12572	(12553–12572	ACAACCCAGCTCTCCCTAAG	591	56
H13124	(13143–13124	ATTTTCTGCTAGGGGGTGGA		
L13088	(13068–13088	AGCCCTACTCCACTCAAGCAC	618	58
H13666	(13685–13666	AGGGTGGGGTTATTTTCGTT		
L13612	(13593–13612	AAGCGCCTATAGCACTCGAA	614	56
H14186	(14206–14186	TGGTTGAACATTGTTTGTTGG		
L13612	(13593–13612	AAGCGCCTATAGCACTCGAA	614	56
H14186	(14206–14186	TGGTTGAACATTGTTTGTTGG		
L14125	(14104–14125	TCTTTCTTCTTCCCACTCATCC	602	58

Table 2: Oligonucleotide pairs used in the amplification and sequencing *(Continued)*

H14685	(14705–14685	CATTGGTCGTGGTTGTAGTCC		
L14650	(14629–14650	CCCCATTACTAAACCCACACTC	604	58
H15211	(15232–15211	TTGAACTAGGTCTGTCCCAATG		
L15162	(15143–15162	CTCCCGTGAGGCCAAATATC	597	58
H15720	(15739–15720	GTCTGCGGCTAGGAGTCAAT		
L15676	(15657–15676	TCCCCATCCTCCATATATCC	524	56
H16157	(16180–16157	TGATGTGGATTGGGTTTTTATGTA		
L15996	(15975–15996	CTCCACCATTAGCACCCAAAGC	446	58
H16401	(16420–16401	TGATTTCACGGAGGATGGTG		

Conclusions

After coming out of Africa, modern humans first spread to Asia following two main routes. The southern one is represented by haplogroup M and related clades that are overwhelmingly present in India and eastern Asia. The northern one gave a posterior radiation that, through Central Asia, again reached North and East Asia carrying, among others, the prominent lineages A and B. Later expansions, can be detected by the presence of subclades of haplogroup U in India and Europe. There were also returns to Africa, most probably from the same two routes. The return from India could be detected by the presence of derivatives of M in Northeast Africa, and the arrival of Caucasoids by the existence of a subclade of haplogroup U that, today, is mainly confined to Northwest Africa.

Materials and Methods

Lineages

We have manually sequenced 33 complete mtDNA genomes from available samples previously assigned to major haplogroups. To include lacking haplogroups we added 9 published sequences to the analyses (Table 1).

Complete mtDNA sequences

Complete mtDNA were amplified in 32 overlapping fragments with primers and PCR conditions described in Table 2. The same primers were utilized to directly sequence both strands of the fragments using the Promega fmol® DNA Cycle Sequencing System and the Usb Thermo Sequenase Radiolabelled Terminator Cycle Sequencing Kits.

Statistic analyses

Sequences were aligned manually. Phylogenetic relationships were estimated using median-joining networks [32] as implemented in Network 2.0d [http://www.fluxus-engineering.com] and refined by hand. The same topology was obtained using the neighbor-joining method [33]. A chimpanzee sequence (GenBank accession n° D38113) was added to root the networks. Statistical significance of the branches were accomplished by bootstrap resampling with 1000 replications (PHYLIP Package 3.5c, [http://evolution.genetics.washington.edu/phylip.html]). Minimum estimates of coalescence ages, and 95% confidence intervals, were based on mean divergence among lineages for the coding region and a constant evolutionary rate of 1.7×10^{-8} per site per year that has been inferred for this region on the basis of 53 complete mtDNA sequences [7].

Accesion numbers

Sequences are available in GenBank (accession nos. AF381981-AF382013)

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