Divergence of East Asians and Europeans Estimated Using Male- and Female-Specific Genetic Markers

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Data deposition: We collected the complete mtDNA genomes (16,750 bp each) from the International Nucleotide Sequence Data Collaboration (DDBJ/EMBL/GenBank) to study the female lineage of the Europeans and East Asians.

Abstract

To study the male and female lineages of East Asian and European humans, we have sequenced 25 short tandem repeat markers on 453 Y-chromosomes and collected sequences of 72 complete mitochondrial genomes to construct independent phylogenetic trees for male and female lineages. The results indicate that East Asian individuals fall into two clades, one that includes East Asian individuals only and a second that contains East Asian and European individuals. Surprisingly, the European individuals did not form an independent clade, but branched within in the East Asians. We then estimated the divergence time of the root of the European clade as ~41,000 years ago. These data indicate that, contrary to traditional views, Europeans diverged from East Asians around that time. We also address the origin of the Ainu lineage in northern Japan.

Key words: human evolution, individual lineages, mitochondrial DNA, Y-STR, East Asians, Europeans.

Introduction

The study of human evolution has benefited from the development of genome-wide approaches to obtaining molecular data. However, most genes in the genome do not evolve fast enough for the study of human evolution at the level of direct sequence comparisons, for which reason short tandem repeat (STR) markers on the Y chromosome (Y-STR) and mitochondrial DNA sequence (mtDNA), both of which evolve faster than autosomal loci, are useful in human evolution studies. Those two types of sequences also permit the independent study of male and female lineage divergences. Y-STR and mtDNA data have thus contributed to elucidating many aspects of human evolution (Cann et al. 1987; Excoffier et al. 1987; Bowcock et al. 1991; Horai 1991; Excoffier et al. 1992; Cavalli-Sforza et al. 1994; Hammer and Horai 1995; Zerjal et al. 1997; Bergen et al. 1999; Shinka et al. 1999; Tanaka et al. 2004; Katoh et al. 2005a; Derenko et al. 2007). In addition, while Ingman et al. (2000) and Maca-Meyer et al. (2001) have shown that mtDNA sequences are still appropriate for the studies of global human diversity, Katoh et al. (2005b) demonstrated the usefulness of Y-STR for the evolutionary study of East Asian ethnic groups.

However, those studies have lacked resolution for individual lineages and have not provided coherent pictures of male and female lineage splittings. Indeed, a major issue in human evolution is that the study of the male lineage delivers results that differ from those obtained through the study of the female lineage (Underhill and Kivisild 2007). Therefore, we focused in the present study on examining human evolution at the level of males and females separately. Our interest...
focused on the divergence of three major populations—Africans, Europeans, and East Asians—and East Asians and Europeans in particular, because they lived together for a while after coming out of Africa and likely interbred, perhaps similar to the hybridizations reported between Neandertals and modern humans (Noonan 2006). After the divergence between Mongoloid (East Asian) and Caucasoid (European) people ~55,000 years ago (Nei and Roychoudhury 1993), they might have still interbred while en route to settlement in their present localities.

To investigate this, we sampled a number of European and East Asian individuals to obtain information on the male and female lineages, by constructing phylogenetic trees based on Y-STR and mtDNA sequences, respectively. These two trees should provide new information on the divergence of the East Asian and European lineages. We included in our study data from the Ainu people in the northernmost island of the Japanese archipelago, because their ancestor and evolutionary history are still obscure. Recently, Jinam et al. (2012) suggested that the Ainu are closer to the people in Okinawa from the southmost archipelago in Japan than they are to any other East Asian people. Our investigation also addresses Ainu origin.

Materials and Methods

Population Samples

To study male lineages, we sequenced and analyzed Y-STR for 453 unrelated males, which were classified into 242 Japanese, 85 Korean, 77 Khalkh Mongolian, and 49 European bins. The Korean samples were collected in Seoul, while the Khalkh Mongolian samples were obtained in Ulaanbaatar, Mongolia (Katoh et al. 2002, 2005a, 2005b). The Khalkh are the major population in Mongolia, representing ~80% of the total population, the language spoken in Mongolia has its origins in the Khalkh language. The European samples were collected from the Coriell Cell Repositories (Human variation panel, Caucasoid, HD100CAU). Informed consents were obtained from donors at each laboratory or institution. For the genetic study of these samples, we obtained permission from the ethics committee of Tokai University, Japan.

Y Chromosome Binary Markers

We typed 453 male individuals for a total of 14 binary markers on the Y chromosome. These markers were M130, YAP, M15, M57, SRY-4064, M89, M9, M128, Tat, M175, M119, SRY+465, M122, and M45. M130 was typed by polymerase chain reaction (PCR) amplification using the primers described in Bergen et al. (1999), followed by BstI digestion. YAP, SRY-4064, Tat, and SRY+465 were typed according to Hammer and Horai (1995), Bravi et al. (2000), Zerjal et al. (1997), and Shinka et al. (1999), respectively.

For the indel markers, M15, M57, M128, and M175, we performed PCR amplification with the primers described in Underhill et al. (2001), labeling the 5′ end of the forward primer with a fluorescent marker. For M89, M9, M122, M119, and M45, we carried out allele-specific PCR assays according to the primer designs of Su et al. (1999). These markers consisted of two forward primers, which defined SNP alleles, and one reverse primer. We labeled the 5′ end of each forward primer with a different fluorescent dye (FAM and HEX). PCR reactions were performed in a 10-μl reaction volume, containing 1× AmpliTaq PCR buffer with 1.5 mM MgCl₂ (Applied Biosystems), 200 μM each of dNTP, 0.25 U AmpliTaq polymerase (Applied Biosystems), 1 pmol of each primer, and 6 ng of genomic DNA. The cycle conditions were as follows: 94°C for 2 min; followed by 30 cycles of 94°C for 30 s, 54–62°C for 30 s, and 72°C for 50 s; followed by a 5-min extension at 72°C. The amplified products were detected using the ABI Prism 3700 DNA analyzer.

Y-STR Genotyping

We used 25 STR markers on the Y chromosome: DYS388, DYS389I, DYS389b, DYS390, DYS391, DYS392, DYS393, Y-GATA-A7.1 (DYS460), Y-GATA-A7.2 (DYS461), Y-GATA-A10, Y-GATA-C4, Y-GATA-H4, DYS597, DYS598, DYS599, DYS600, DYS601, DYS602, DYS603, DYS604, DYS605, DYS606, DYS607, DYS608, and DYS609. We labeled the 5′ end of each forward primer with a fluorescent dye (FAM or HEX), and a PCR reaction for each marker was carried out independently. PCR reactions for DYS388, DYS389I, DYS389b, DYS390, DYS391, DYS392, and DYS393 were performed according to published procedures with minor modifications (Kayser et al. 1997). PCR reactions for the remaining 18 markers were carried out in a total volume of 10 μl, containing 10 mM Tris–HCl, pH 8.0, 50 mM KCl, 2.0 mM MgCl₂, 0.01% gelatin, 200 μM each of dNTP, 0.3 U AmpliTaq polymerase (Applied Biosystems), 2 pmol of each primer, and 6 ng of genomic DNA. These markers were amplified by the following cycling conditions: pre-PCR of 5 min at 96°C, 1 min at 57°C, and 1 min at 72°C; followed by 30 cycles of 96°C for 45 s, 57°C for 45 s, and 72°C for 1 min; with a final extension at 72°C for 5 min.

Amplicons were separated using the ABI Prism 3700 DNA analyzer, and allele sizes were calibrated with the GeneScan 500 ROX size standard. Fragment sizes were determined using GenScan Analysis 3.5 and Genotype 3.5NT software (Applied Biosystems). The number of repeat units in each fragment was determined by sequencing reference DNA samples with different alleles. The alleles were designated with repeat numbers. The allele length for DYS389b was obtained by subtracting the allele length of DYS389I from that of DYS389II (Qamar et al. 2002; Zerjal et al. 2002).

Data Analysis

Y-chromosome binary haplogroups for the four human populations mentioned earlier were defined by the analysis of all
14 binary markers. The nomenclature of haplogroups followed that of the Y chromosome consortium (Slatkin 1995) and Karafet et al. (2008). Then, a Y-STR haplotype tree for the 453 male individuals and a mtDNA tree for the 72 individuals were constructed by using the neighbor-joining (NJ) method (Saitou and Nei 1987) in the MEGA 5.0 (Tamura et al. 2011).

The distance computed for the Y-STR tree was the $R_{ST}$ distance (Slatkin 1995) between a pair of Y-STR haplotypes. For haplotypes $x$ and $y$, we computed the distance ($d$) between them by using the formula

$$d = \frac{1}{n} \sum_{i=1}^{n} (x_i - y_i)^2,$$

where $n$ is the number of loci, $x_i$ and $y_i$ are the number of repeats of the $i$th locus of the haplotypes $x$ and $y$, respectively (fig. 1).

To study the female lineages we collected the complete mtDNA genomes (16,750 bp each) from the International Nucleotide Sequence Data Collaboration (DDBJ/EMBL/GenBank) to study the female lineage of the European and East Asian. The mtDNA genome data include 32 Japanese, 11 Korean, 5 Mongolian, 23 European, and 1 African samples (table 1). For the mtDNA tree the evolutionary distance between a pair of individuals was obtained by the Kimura two-parameter method (Kimura 1980). The bootstrap test (Felsenstein 1985) was performed for 1,000 replicates for each tree (fig. 2). The African sample was used as the reference in the phylogenetic trees.

**Results**

For the male lineages, we used the Y-STR markers for 453 individuals covering Japanese, Korean, Mongolian (Khalkh), American, and European people. We determined the evolutionary distances ($R_{ST}$) among them, and constructed a phylogenetic tree using the NJ method (Saitou and Nei 1987), as shown in figure 1. The Y-STR tree revealed that the male ancestral lineage contained two clades (Yap-A and Yap-B). While Yap-A clade includes the East Asian individuals only, Yap-B clade contains the East Asian and European individuals together. Surprisingly, the European males never formed an independent clade. Instead, they formed separate clades within Yap-B.

We then constructed a phylogenetic tree (Mt tree) for the 72 complete mtDNAs including the four ethnic groups, as shown in figure 2. We used Kimura’s two parameter method (Kimura 1980) for computing evolutionary distances among them and the NJ method for the tree construction. The Mt tree revealed two female descendant clades (Mt A and Mt B). Mt B consisted of the East Asian females only, while Mt A clade includes the East Asian and European females together. As in the case of males, the European females did not form an independent clade, but comprised several groups within the Mt A tree. As the Mt A cluster includes roughly as many European individuals as East Asian individuals, it is not clear which of them is ancestral to the other. The node marked with the blue circle in figure 2 suggests that the East Asians are ancestral to the Europeans. The bootstrap value of the node
that R years ago (Nei and Roychoudhury 1974, 1993), and assuming Based on a divergence of East Asians from Africans of 55,000 root of the European male clade in the B clade was 12.31. The rate is thus estimated as 16.91/ and that between the common ancestor of Europeans males and root in any route was 0.00132 per nucleotide site, while In the case of the Mt tree, we first transformed it into tree (Sokal 1958), because we now dealt with the evolutionary time rather than distance (Kumada 1993). In the transformed tree, the topology was kept unchanged. We call the transformed tree the evolutionary time (ET) tree (fig. 3), because the tree reflects the evolutionary time rather than the distance, we call the tree showing evolutionary distance the evolutionary distance (ED) tree. In the present ET tree, the distance between the bottom and root in any route was 0.00132 per nucleotide site, while that between the bottom and the root (marked with the closed circle) of the European male clade was 0.000996. Therefore, assuming again that the two major clades in the Mt tree diverged from the African ~55,000 years ago, we estimated the evolutionary rate of mtDNA as 2.4 × 10⁻⁸ per site per year. Our estimate was comparable with that of Ingman et al. (2000). It is noted that our estimate for the human mitochondrial genome is more than ten times faster than that of the human nuclear neutral sequences (Fukami Kobayashi 2005). Then, by applying the evolutionary rate of mtDNA to the distance between the bottom and root in the European clade, we estimated the divergence time of the European females, as ~41,500 years ago. Thus, both the Y-STR and Mt trees are mutually consistent with respect to the tree shape and divergence time of European individuals relative to East Asians, despite being based on independent data and distance measures. Our results suggest that the European people settled down in their territories ~41,000 year ago, and have developed their own cultures and languages since then. On the other hand, the East Asians were classified into two clusters; one is Type 1 East Asians denoted as Yap-A and Mt clusters in the male and female trees, respectively, and the other is Type 2 East Asians denoted as Yap-B and Mt A clusters in the male and female trees, respectively. While Type 1 includes East Asian individuals only, Type 2 contains East Asians and European individuals together. The general view of the East Asian and European divergences is summarized in figure 4.

### Table 1
List of Accession Number for Mitochondrial Genomes Analyzed in This Study

| Group Name | Accession Number |
|------------|------------------|
| Japanese 32 | AP008912, AP010835, AP010837, AP008691, AP010664, AP008279, AP008852, AP008751, AP010834, AP008837, AP010832, AP008791, AP008276, AP008270, AP008280, AP008274, AP008705, AP008301, AP008283, AP008777, AP010831, AP008267, AP008272, AF346990, AP010663, AP010676, AP008768, AP008302, AP008303, AP010830, AP008706, AP008627 |
| Caucasian 23 | EU600323; France Druze, JQ343921; France, GQ200588; USA, GU294854; Canada, HQ398469; USA, JQ048704; Portugal, KG618506; England: Devon, NC 01920; Great Britain, FJ216960; Europe, HQ729918; France: Brittany, HQ610202; USA, GU323604; Ireland, KC649897; England Worcestershire, KC682980; England: Liverpool, GQ129173; Spain: Southern Spain, AY275537; Spain: Canary Islands, AY275530; Spain: Galicia, HQ025914; USA, HQ615683; Portugal, HQ651702; Portugal, HQ651697; Portugal, HQ585390; USA, HQ651686; Portugal |
| Korean 11 | AF346993, EF153824, EF153823, EF397561, FJ951594, EF153822, EF153821, FJ951589, FJ951590, FJ951592 |
| Mongolian 5 | EU007891, EU007892, AY255146, EU007893, EU007890 |
| African 1 | AF346995 |

is 99%. Therefore, both male and female lineages suggest that Europeans diverged from within East Asian ancestors or that they interbred with East Asian individuals up to a certain divergence time. Our next question was thus to estimate the divergence time of the European clade within the East Asian lineage, for males and females separately. To address that question, we computed the evolutionary distance (RST) between every pair of the male individuals to construct the Y-STR tree in figure 1. The RST value between the bottom and root of A and B clades in the tree was 16.91, while that between the bottom and root of the European male clade in the B clade was 12.31. Based on a divergence of East Asians from Africans of 55,000 years ago (Nei and Roychoudhury 1974, 1993), and assuming that RST is proportional to time, we can estimate the evolutionary rate of Y-STR by using the Y-STR tree. In the tree the RST value between the deepest root and the bottom is 12.31. The rate is thus estimated as 16.91/ 

4 per repeat per year, which leads us to the conclusion that the divergence time of the European males is ~40,100 years ago.

In the case of the Mt tree, we first transformed it into tree in which the lengths of a pair of branch lengths from the common node were equal to one another, as in the UPGMA tree (Kobayashi 2005). Then, by applying the evolutionary rate of mtDNA to the distance between the bottom and root in the European clade, we estimated the divergence time of the European females, as ~41,500 years ago.

Both the Y-STR and mtDNA trees consistently show that Europeans diverged from East Asian ancestors ~41,000 years ago. Population genetic theory indicates that 41,000 years, or about 2,000 generations, are long enough to accumulate SNPs in the same loci in each lineage (Kimura 1983; Nei 1987) to account for the present genetic and phenotypic differences between the East Asians and Europeans, but too short to acquire independent loci between them.

**Discussion**

Both the Y-STR and mtDNA trees consistently show that Europeans diverged from East Asian ancestors ~41,000 years ago. Population genetic theory indicates that 41,000 years, or about 2,000 generations, are long enough to accumulate SNPs in the same loci in each lineage (Kimura 1983; Nei 1987) to account for the present genetic and phenotypic differences between the East Asians and Europeans, but too short to acquire independent loci between them.
MtA

MtB

Red: European
Blue: East Asian

Fig. 2.—Phylogenetic tree of the complete mitochondrial genomes for the four ethnic groups. It is divided into MtA and MtB. MtA contains East Asian and European individuals together while MtB includes East Asian individuals only.
Fig. 3.—A phylogenetic tree of the complete mitochondrial genome (16,750 bp) including D-loop regions of 72 humans; 32 Japanese, 11 Korean, 5 Mongolian, 23 European, and 1 African samples. This phylogenetic tree was constructed using the UPGMA method by the MEGA 5.0 version program.
Recently, Liu (2012) reported on five genes responsible for the facial morphology of European people. The East Asian people must have the counterparts that differ at the SNP level from those in the European people. As our phylogenetic trees demonstrate, the European alleles at the five loci have diverged from the ancestral East Asian alleles.

Our result contrasts with the traditional view that Europeans and East Asians simultaneously diverged from African ancestors 55,000 years ago. It is noteworthy, however, that Shinoda (2007) investigated into the haplogroups of mtDNA, and revealed a number of evolutionary haplotype lineages. The lineages include L3 (African), N (East Asian), W (European), and L3 to N to R (East Asian) and then HV (European) among others. Though they did not explain their results, their haplotype lineages can now be understood by our finding that the Europeans diverged from the East Asians. Therefore, the discrepancy between the traditional view and ours lies mainly in that the traditional view was based on autosomal genes that evolved much slower than Y-STR or mtDNA, and could not distinguish the evolutionary lineages at the individual level. Note that, as estimated earlier, the evolutionary rate of mtDNA is $2.4 \times 10^{-8}$ per site per year, while that of nuclear neutral sequences is $2.0 \times 10^{-9}$ per site per year (Fukami Kobayashi 2005). The discrepancy also is due to the fact that while we dealt with many male and female individuals in our study, the other studies did not.

By typing the 14 binary markers of the Y-STR sequences according to the classification agreed at the Y Chromosome Consortium (2002) and elsewhere (Karafet et al. 2008), we found that all individuals in the Yap-B1 in figure 1 belonged to either haplogroup C or D, while the majority in the Yap-B2 belonged to haplogroup O. Since Yap-B1 includes mainly Japanese and Korean males, in which 91% individuals share haplotype O2b, the Korean and Japanese males are definitely closest to one another within East Asian humans. We also found a high frequency of the O2b haplotype in Manchu (Northern China) and Korean-Chinese samples (Katoh et al. 2005b; Kim et al. 2011).

The origin of the Ainu people is still an unresolved issue (Tajima et al. 2004). On the basis of our results, we propose a possible scenario for the origin of the Ainu people, who now live in the north-most island of the Japanese archipelago, Hokkaido. The Ainu people have European phenotypic characters, but they are genetically closer to East Asians than to Europeans (Watanabe 1975). These contradictory features of the Ainu people are puzzling. As shown in figure 4, Europeans may have diverged from East Asians ~41,000 years ago, it is possible that hybrid individuals were born before the divergence, and some of them looked more like the Europeans while possessing a generally East Asian genotype. We suggest that the ancestor of the Ainu people was such a group of the hybrid individuals. We note that the present Ainu people share the mtDNA haplotype not with the Japanese but with the European living in Siberia, Russia (Adachi et al. 2009). Thus, we furthermore suggest that the ancestor of the Ainu originated in northern Eurasia and took a route through Siberia and north China before settling in northern regions of Japan and nearby places. There is a report that other people than the Ainu also lived in the northern regions but disappeared (Adachi et al. 2009). As the people in Okinawa islands are closest to the Ainu people in the East Asians (Jinam et al. 2012), they might also be descendants from of mixing of East Asian and European lineages.

**Conclusion**

Humans are traditionally viewed as falling into three major populations, Africans, East Asians, and Europeans, with the latter two diverging from the African ancestors ~55,000 years ago. We sequenced Y-STR makers in Y chromosome and collected complete mtDNAs for many East Asian and European individuals to reexamine that view. Phylogenetic trees of Y-STR makers and Mt genes suggest that the Europeans interbred with East Asians until ~41,000 years ago. On the other hand, East Asians diverged from their African ancestors ~55,000 years ago. Therefore, we suggest that the European and East Asian lineages diverged ~41,000 years ago.

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