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RESEARCH ARTICLE

Mitochondrial DNA sequence variation in the Anatolian Peninsula (Turkey)

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Abstract

Throughout human history, the region known today as the Anatolian peninsula (Turkey) has served as a junction connecting the Middle East, Europe and Central Asia, and, thus, has been subject to major population movements. The present study is undertaken to obtain information about the distribution of the existing mitochondrial D-loop sequence variations in the Turkish population of Anatolia. A few studies have previously reported mtDNA sequences in Turks. We attempted to extend these results by analysing a cohort that is not only larger, but also more representative of the Turkish population living in Anatolia. In order to obtain a descriptive picture for the phylogenetic distribution of the mitochondrial genome within Turkey, we analysed mitochondrial D-loop region sequence variations in 75 individuals from different parts of Anatolia by direct sequencing. Analysis of the two hypervariable segments within the noncoding region of the mitochondrial genome revealed the existence of 81 nucleotide mutations at 79 sites. The neighbour-joining tree of Kimura's distance matrix has revealed the presence of six main clusters, of which H and U are the most common. The data obtained are also compared with several European and Turkic Central Asian populations.

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Introduction

The Anatolian peninsula, known today as Turkey, consists of a high plateau that is contiguous with the steppes of central Asia. The northern part of Anatolia (Black Sea region) is a mountainous area with a steep and rocky coast, and rivers cascading through the gorges of the coastal ranges. As the northern Anatolian Mountains run parallel to the coastline, access inland from the coast is limited with fewer valleys, isolating the coast from inland areas. The northwest part of Anatolia covers the European part as well as the northwest of the Anatolian plain. The mountains run perpendicular to the coastline in the west. The western and central Taurus Mountains rise up through the coastline in the south of Anatolia (Mediterranean region). The Central Anatolian Region is a plateau in the middle of Turkey and is less mountainous when compared with the other regions. The eastern part of Anatolia is the largest and highest region, and Anatolia's highest peak Mount Ararat is located in this region. This is the most thinly populated region of the country (Yenen 1998). Anatolia has been home to many great civilizations including Hattis, Hittites, Phrygians, Urartians, Lycians, Lydians, Ionians, Persians, Macedonians, Romans, Byzantines, Seljuks and Ottomans since 6500 B.C. (Roux 1998). The Turks arrived in Anatolia in the 11th century A.D., from their homeland between the Ural Mountains in Europe and the Altay Mountains in Asia (Güvenç 1997). Turks who live in Anatolia speak a language that belongs to the Turkic branch of the Altaic family. The Anatolian peninsula has been occupied by numerous Mediterranean, Middle Eastern and Asian populations in the past. Hence, there is reason to believe that considerable genetic variations may exist within the present population of Anatolia.

Several studies have attempted to analyse mtDNA sequences in various Turkish populations (Calafell *et al*. 1996;

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Comas *et al*. 1996; Richards *et al*. 1996). These studies, however, were conducted with small sample sizes and did not give a detailed account of the origins of the study populations. Therefore, they may not properly reflect the possible genetic heterogeneity of the Anatolian population. In this study, we extend previous observations by analysing mtDNA sequences of two hypervariable segments in a larger cohort consisting of individuals from various geographical regions of Turkey, which is thus more representative of the Turkish population living in Anatolia.

Materials and methods

Study population

The study population consisted of 75 unrelated healthy individuals. In order to obtain a representative cohort for the country, samples were obtained from individuals coming from five distinct geographical regions of Turkey (figure 1). The numbers of the samples collected from each region are 17 from north, 15 from east, 14 from central, 15 from south, and 14 from west Anatolia.

DNA extraction and PCR

Total DNA was isolated from the blood samples as described previously (Mergen *et al*. 2000). Asymmetric amplification of the two hypervariable segments of the noncoding region was accomplished by using the following primers in unequal concentrations: L15926 (forward; 5′-TACACCAGTCTTGTAAACCGGAGA-3′) and H16421 (reverse; 5′-TTGATTTCACGGAGGATGGTGG-3′) for the HVS I region, and L16471 (forward, 5′-GGGTAGCTAAAGTGAACTGTA-3′) and H00580 (reverse, 5′-TGCTTTGAGGAGGTAAGCTACATA-3′) for the HVS II region. Each 100 µl of PCR reaction mixture contained approximately 100 ng of DNA, 2 pmol of forward primer, 100 pmol of reverse primer, 200 mM of each of the dNTPs, 1 × PCR buffer provided with the enzyme *Taq* polymerase by the manufacturer, and 2.5 units of *Taq* polymerase. PCR was conducted in a thermal cycler using 30 cycles, denaturation at 94°C for 45 s, annealing at 56°C for 1 min, and polymerization at 72°C for 1 min and 30 s.

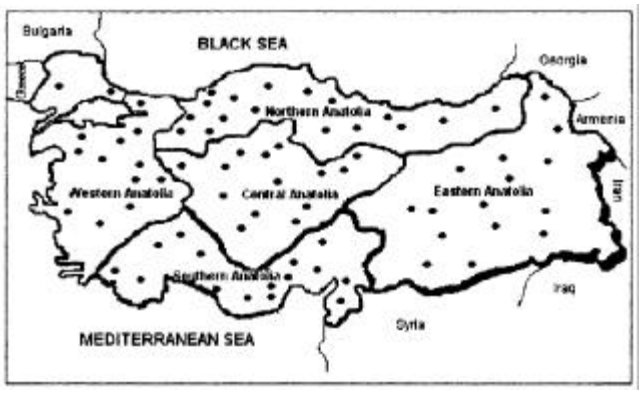

Figure 1. Map of the Anatolian peninsula (Turkey), showing the distribution and origins of the samples.

DNA sequencing and data analysis

Asymmetrically amplified DNA product was precipitated and sequenced directly using the USB Sequenase Version 2.0 kit and ^{35}S-dATP. Approximately 300 nucleotides in the HVS I region (between the nucleotides 16040 and 16340) and 300 nucleotides in the HVS II region (between the nucleotides 16510 and 295) were analyzed.

Phylogenetic analysis was performed using the PHYLIP 3.5c software package (Felsenstein 1989). Alignment was performed either by hand or with ClustalX (Higgins and Sharp 1988). To estimate the relationship between the sequences, genetic distances between haplotypes were calculated using the two parameter model of Kimura with the transition-transversion ratio set to 10 : 1 (Kimura 1980). The neighbour joining trees were constructed using the HVS I and HVS II sequences for Turks, and HVS I sequences of the individuals from Turkish and other populations, using the NEIGHBOUR program in the PHYLIP 3.5c software package (Saitou and Nei 1987; Felsenstein 1989). Trees were drawn using the DRAWTREE and DRAWGRAM programs, 1000 bootsrap data sets were obtained using SEQBOOT, and consensus trees were obtained using the CONSENSE program provided with the PHYLIP 3.5c software package (Felsenstein 1989).

The data from other populations used for comparison include British (n = 30) (Piercy *et al*. 1993), Greek (n = 50) (Kouvatsi *et al*. 2001), Bulgarian (n = 30) (Calafell *et al*. 1996), German (n = 30) (Hoffman *et al*. 1997), Finnish (n = 28) (Sajantila *et al*. 1995), French (n = 30) (Rousselet and Mangin 1998), and Turkic Central Asian (Kazakhs, Uighurs and Kirghiz) (n = 145) populations (Comas *et al*. 1998). Genetic distances between the populations were also computed using Nei's (1972) distances, and the population tree was constructed using the HVS I sequences for Turks and other populations using the POPGENE Version 1.31 software package (Yeh *et al*. 1999). Genetic structure among the Turkish individuals was compared by using the Analysis of Molecular Variance program (AMOVA) in the ARLEQUIN package (Schneider *et al*. 1996).

Results

Sequence diversity

The DNA sequences of the two hypervariable segments of the mtDNA D-loop region in the 75 unrelated Turkish individuals were compared to the reference sequence reported by Anderson *et al*. (1981), and the results are summarized in figure 2. We detected a total of 81 nucleotide alterations at 79 sites in the two hypervariable regions, of which

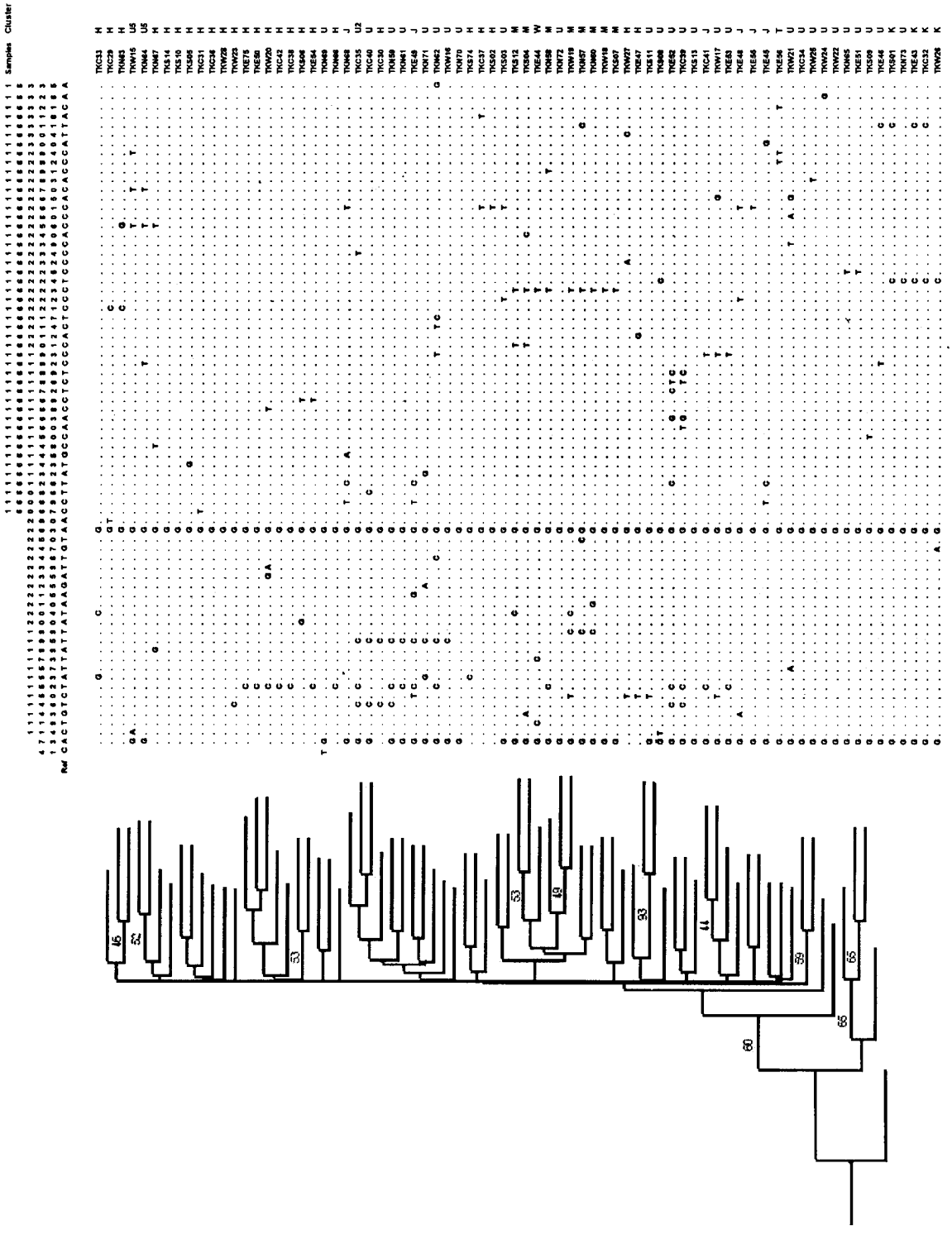

Figure 2. Neighbour-joining tree of the Turkish population and variable positions of the mitochondrial control regions in 75 Turkish samples. Ref. denotes the Cambridge Reference Sequence (Anderson *et al*. 1981), and those sequences directly derived from it. A dot indicates the presence of the same nucleotide as in the reference sequence. The symbols TKE, TKN, TKW, TKS and TKC before the numbers represent the regions of eastern, northern, western, southern and central Anatolia, respectively.

Table 1. Frequency of the clusters found in Turkish samples.

Regions	Clusters; no. (%) of sequences								
	H	U	K	U2	U5	J	T	M	W
Northern Anatolia	3(17.6%)	9(52.9%)	–	–	1(5.8%)	1(5.8%)	–	2(11.7%)	1(5.8%)
Southern Anatolia	6(40%)	5(33.3%)	1(6.6%)	–	–	–	–	3(20%)	–
Western Anatolia	4(28.5%)	6(42.8%)	1(7.1%)	–	1(7.1%)	–	–	2(14.2%)	–
Central Anatolia	8(57.1%)	3(21.4%)	1(7.1%)	1(7.1%)	–	1(7.1%)	–	–	–
Eastern Anatolia	4(26.6%)	4(26,6%)	1(6.6%)	–	–	4(26.6%)	1(6.6%)	1(6.6%)	–
Total	25(33.3%)	27(36%)	4(5.3%)	1(1.3%)	2(2.6%)	6(8%)	1(1.3%)	8(10.6%)	1(1.3%)

11 have not been previously reported. Of the 79 sites, 52 were in the HVS I region and 27 were in the HVS II region. As expected, transitions were more common than transversions. While the transitions (C ↔ T, A ↔ G) were observed at 68 sites, the transversions (C ↔ G, A ↔ C, A ↔ T, T ↔ G) were detected only at 13 sites. Insertion / deletion events were not observed. As in several Caucasoid populations, all the samples sequenced in this study also showed a variation from the reference sequence at position 263 and had guanine instead of adenine (Anderson *et al*. 1981). As pointed out by Calafell *et al*. (1996), the reference sequence is the only one where the nucleotide at position 263 in segment II is an adenine.

The sequence variation obtained in our gene pool was sufficient to allow the construction of several clusters, which have been named according to the accepted norms of Macaulay *et al*. (1999). Six distinct major clusters, namely H, J, T, M, U and W, were observed in our population. The frequency of the clusters is given in table 1. Other clusters, known as I, X, C and V, and four subclusters of U (U1, U3, U4, and U6) which were defined in other populations, were not observed in our gene pool. The cumulative frequency of European specific clusters (H, J, T and W) was 43.9% and Asian specific cluster (M) was 10.6% in our population (table 1).

The polymorphisms 16069T, 16126C, 16163G, 16169T, 16186T, 16189C, 16193T, 16221T, 16223T, 16224C, 16225T, 16256T, 16261T and 16311C observed with different combinations in Turkish population are given in table 2. These HVS I sequence motifs were compared with European and central Asian populations (Richards *et al*. 1996; Comas *et al*. 1998) (table 2). The polymorphisms 146C, 150T, 152C, 195C, 199C are the most common polymorphisms in the HVS II region in Turkish population (table 3). All three samples having 199C in HVS II region are in the cluster M. Six individuals who have A at nucleotide 00073 (cluster H) have only one polymorphism at nucleotide 152. Nucleotide diversity was estimated to be 0.0147 in Central Anatolia, 0.0151 in Eastern, 0.0146 in Northern, 0.0130 in Southern and 0.0119 in Western Anatolia.

Pairwise differences

Pairwise difference distributions for the individuals from 5 different regions of Anatolia are given in figure 3. For segments I and II, samples from the central and northern Anatolia present peaks at 3 and 4 differences, with means of 4.29 ± 0.760 and 3.62 ± 0.850 differences, respectively. The samples from eastern Anatolia region had five peaks at 1, 2, 3, 5 and 6 with a mean of 4.42 ± 0.556 differences. The samples from western Anatolia region show two peaks at 2 and 4 with a mean of 4.56 ± 0.590 differences, and samples from southern Anatolia region present one peak at 3 with a mean of 3.45 ± 0.685 differences. Cumulatively considered, all samples except western Anatolia present one peak at 3 for segments I and II.

Haplotype trees

Genetic distances among the Turkish mtDNA haplotypes were computed for segments I and II. The resulting neighbour-joining tree is shown in figure 2. The data reveal that no cluster of lineages was specific for a given region, and sequences of individuals were scattered throughout the tree. The neighbour-joining tree that include haplotypes for segment I of the European, central Asian and Turkish individuals was constructed with very low bootstrap values for each shown cluster (<40%). Once again, sequences of individuals from different populations were mainly scattered throughout the tree (data not shown).

Population tree

Genetic distances between populations were estimated according to the Nei's (1972) method (table 4). The neighbour-joining tree built from segment I sequences for Turkish and the other populations (French, Bulgarian, British, Finland, Greek, German, Kazakhs, Uighurs and Kirghiz) showed two poles. Turkic central Asian populations, Turkish population and British population formed one pole, and European populations formed the other. Turkish popu-

lation bore similarities to Turkic central Asian population (figure 4).

Discussion

In this study, we have determined the nucleotide sequence of the mitochondrial control region from 75 unrelated Turkish individuals from southern, northern, western, eastern and central parts of Anatolian peninsula. Our analysis showed the presence of six distinct clusters; H, J, T, M, U and W. Cluster H (A at nt 00073), which is the most common cluster in the European population (Richards *et al*. 1996), was also common in our population. The overall frequency of this cluster in Turkey was 33.3%, with the highest frequency in Central Anatolia (57.1%). The cluster H was attributed to reach its highest frequencies (40–60%) in western and northern Europe. This cluster is also common in the Caucasoid populations of the Near East and North Africa, and is also observed in northern India and among Yakuts (Comas *et al*. 1998). Richards *et al*. (1996) reported the frequency of this haplogroup to be 55% in Turkey, a figure similar to what we obtained for Central Anatolia. However, since the origin of the samples is not well defined by Richards *et al*. (1996), it is difficult to compare the two figures. Our findings may support the notion that the origin of haplogroup H is the Near East for most of the European gene pool. This view is also compatible with the presence of haplogroup H in India and Central Asia (Torroni *et al*. 1998).

We found an overall frequency of cluster U to be 36%, with the highest frequency in Northern Anatolia (52.9%). Previous studies have suggested that haplogroup U is much older than the other haplogroups, with an estimated age of 51000–67000 years. It is the only haplogroup that Euro-

Table 2. HVS I sequence motifs defined by different combinations of nucleotides 16069T, 16126C, 16163G, 16169T, 16186T, 16189C, 16193T, 16221T, 16223T, 16224C, 16225T, 16256T, 16261T, 16311C in Turkish[1], central Asian[2] and European[3] sequences.

HVS I sequence motif(s)	Position at nt 00073	No. of sequences in Turkish	Central Asian*	European*	Cluster**
16126, 16069	G	1	0	37	J
16126, 16069, 16300	G	1	0	0	J
16126, 16069, 16261	G	1	0	2	J
16126, 16069, 16261, 16222	G	1	0	0	J
16126, 16069, 16261, 16145	G	1	0	0	J
16126, 16069, 16193	G	1	0	0	J
16126, 16294, 16292 G	G	1	0	3	T
16126, 16186, 16189, 16163, 16172	G	1	0	0	U
16163, 16186, 16189, 16160	G	1	0	0	U
16169	A	2	0	2	H
16193	G	1	1	0	U
16193, 16265	G	1	0	0	U
16193, 16214,1217, 16335	G	1	0	0	U
16221	A	2	0	0	H
16221	G	1	0	0	U
16223	G	4	2	4	M
16223, 16201	G	1	0	0	M
16223, 16201, 16240	G	1	0	0	M
16223, 16291	G	1	0	0	M
16223, 16292	G	1	1	5	W
16223, 16311	G	1	1	0	M
16224	G	1	0	0	U
16225	G	2	0	0	U
16256, 16270	G	1	0	6	U5
16256, 16270, 16294	G	1	0	0	U5
16256, 16148	A	1	0	0	H
16261, 16085	A	1	0	0	H
16261, 16318	A	1	0	0	H
16261, 16222, 16086	G	1	0	0	U
16311, 16192	G	1	0	0	U
16311, 16224	G	4	1	20	K
CRS	A	13			H
CRS	G	9	5	21	U2, U
Unassigned	A	5			H (4), HV (1)
	G	8			U

[1]Present study. [2]Comas *et al*. 1998. [3]Richards *et al*. 1996. *The nucleotide at position 00073 is unknown. **Clusters of Turkish sequences in present study.

peans share with Africans (Simoni *et al*. 2000). Comprehensive analysis of European mtDNAs has suggested that cluster U is composed of at least five subclusters, termed 'U1'-'U5' (Macaulay *et al*. 1999). The frequency of cluster U among the Europeans is approximately 7%, but it appears to be several-fold higher in Finland (Richards *et al*. 1996; Torroni *et al*. 1996). Finnila *et al*. (2000) have recently reported that haplogroup U5 is 30 fold more frequent in Finns than in other European populations (Finnila *et al*. 2000). The relative frequency of cluster U appears to be higher in northern Anatolia compared to European populations except Finland. This observation may suggest that cluster U may have been spread to Europe through northern Anatolia.

We found that the frequencies of nt 16223 (C → T) polymorphism, which is specific for cluster M, are 20%, 11.7% and 14.2% in southern, northern and western Anatolia, respectively. The alteration at nt 16223 is common in east Asia, especially among the Mongoloid people (Horai and Hayasaka 1990), and central Asia (Comas *et al*. 1998). The 16223 alteration was also reported in Africans together with a T → C alteration at nt 16311. We have observed a similar combination in only one individual from northern Anatolia. This combination was also observed in one Turkish individual by Calafell *et al*. (1996) but the sampling region was not clear. Although the 16223 alteration is not generally reported in non-Mongolian populations, the presence of this polymorphism in Turkish population was also reported previously (Calafell *et al*. 1996; Richards *et al*. 1996). This may be due to the fact that Anatolia was strongly influenced by the Mongol invasion in early 14th century A.D.

Our study showed that the frequencies of both nt 16069 (C → T) and nt 16126 (T → C) polymorphisms (cluster J) are 26.6% among the samples from eastern Anatolia. This cluster was previously reported from Middle East (Richards *et al*. 1996). Detection of this unique cluster especially in eastern Anatolia may suggest that the cluster J is confined to the Middle East.

The pairwise difference for segment I and II showed a bell-shaped distribution in northern, southern and central Anatolia (figures 3a,d,e, respectively), and an irregular, multimodal distribution in western and eastern Anatolia (figures 3b,c, respectively). Residents of the eastern Anatolia lead a relatively conservative life style and show a high rate of consanguineous marriages. Western Anatolia, on the other hand, is mostly populated by relatively liberal immigrants who came to the region from Southeast

Table 3. HVS II sequence motifs defined by different combinations of nucleotides, 146C, 150T, 152C, 195C, 199C in Turkish population.

HVS II sequence	Position at nt 00073	Number of Turkish samples	HVS I cluster
146, 152	G	2	U (16160, 16163, 16186, 16189) U (16126, 16160, 16172, 16186, 16189)
146, 152, 195	G	2	U (CRS) U2 (16059, 16234)
146, 195	G	2	U (CRS) and (16086)
146, 195	A	1	H
150	A	2	H (16212) and (16234, 16304)
150	G	1	U (CRS)
150, 197	G	1	U (16193, 16265)
152	A	7	H (CRS in 5 samples and 16169 in 1 sample)
152, 235, 239	A	1	H (16168)
152	G	3	U (161939) J (16069, 16126, 16153, 16193) M (16223, 162919)
152, 195	G	1	U (CRS)
152, 195, 150, 215	G	1	J (16069, 16126)
152, 195, 246	G	1	U (16193, 16214, 16217)
195, 153, 225	G	1	U (16132)
195	G	1	U (CRS)
199, 204, 150	G	1	M (16223)
199, 250	G	1	M (16223, 16311)
199, 210	G	1	M (16223)
CRS	A	9	H
CRS	G	24	U (13), U5 (2), K (3), M (2), J (3), T (1)
Unassigment	A	5	H (4), HV (1)
	G	7	U (3), M (2), J (1), T (1)
Total		75	

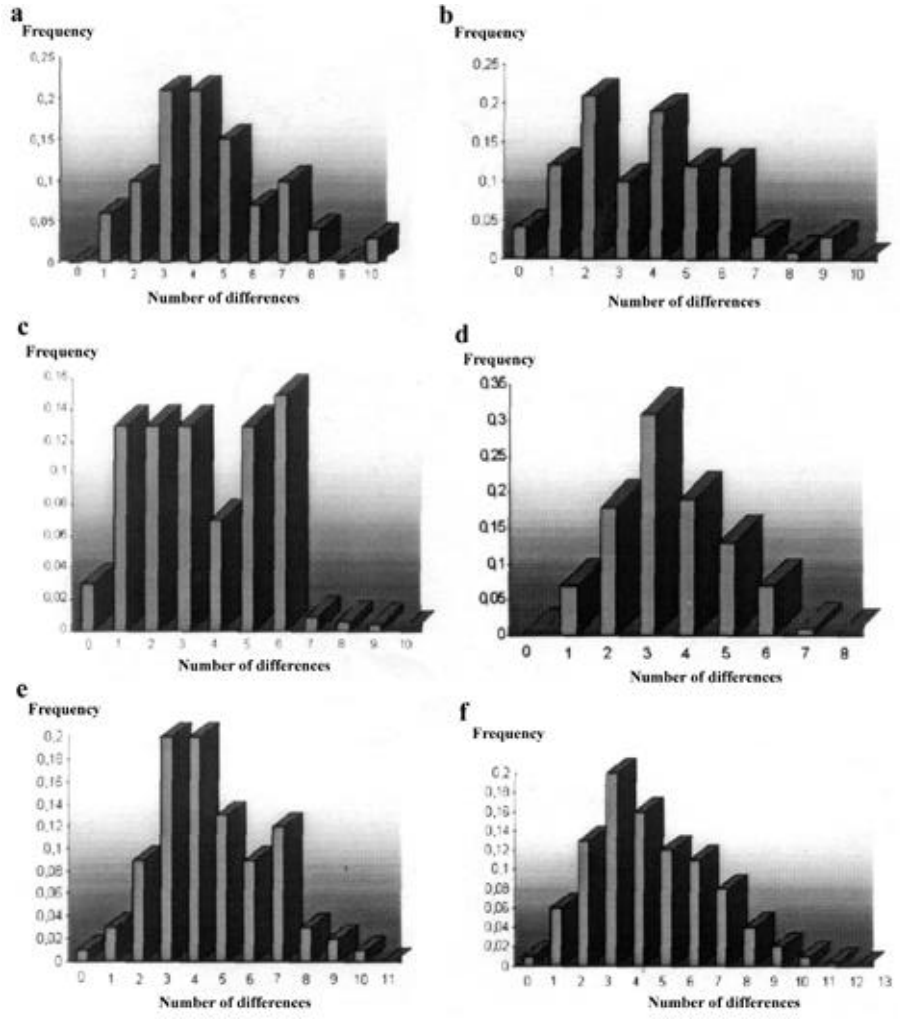

Figure 3. Nucleotide pairwise difference distribution for segment I and II of control region a. The northern part of Anatolia b. The western part of Anatolia c. The eastern part of Anatolia d. The southern part of Anatolia e. The central part of Anatolia f. Turkey.

Europe during Balkan wars. Therefore, there is reason to believe that consanguinity and migration events may be responsible for the observed differences regarding the nucleotide pairwise distributions between Eastern and Western Anatolia. The bell-shaped distribution of the pairwise difference in the whole population (figure 3f) point to the massive movement of people (the Oghuz) from central Asia in the 11th century A.D., and the other migration waves from Middle East through Turkey to Europe.

The neighbour-joining tree constructed from HVS I and II sequences of Turkish individuals showed that no cluster was specific to any region. This result is consistent with the central location and the historical features of Turkey. The neighbour-joining tree built from HVS I sequences of European, Turkish and Turkic central Asian populations showed two opposite poles. Turkic central Asian, Turkish, British and Finnish populations are placed on one side, and German, French, Bulgarian and Greek populations are on the other side of the tree. The historical records show that in the 11th century A.D., Anatolia was occupied by Turkic nomadic groups from central Asia (Benedetto *et al*. 2001), and both Turks and the Turkic central Asian populations (Kazakhs, Uighurs and Kirghiz) speak languages belonging to the branch of the Altaic family. Therefore, it is not surprising that Turkish samples are at a lower distance from Turkic central Asian populations and somewhat higher distance from European populations. Comas *et al*. (1998) reported that Turks present shorter genetic distances to the British than to central Asians. This controversy may be due to the fact that data were obtained from different Turkish samples (Comas *et al*. 1998). In our study, Turkish population has a shorter genetic distance to British than to the other European populations. Observed nucleotide diversity for Turkish population

Table 4. Nei's genetic identity (above diagonal) and genetic distance (below diagonal) between Turkish, European and Turkic central Asian populations, based on hypervariable segment I mtDNA sequences.

	Turkish	French	C. Asians	German	Bulgarian	British	Finnish	Greek
Turkish	****	0.9509	0.9989	0.9503	0.9584	0.9994	0.9756	0.9506
French	0.0504	****	0.9502	0.9991	0.9923	0.9508	0.9277	0.9994
Central Asians	0.0011	0.0510	****	0.9498	0.9577	0.9988	0.9753	0.9501
German	0.0510	0.0009	0.0515	****	0.9918	0.9504	0.9273	0.9992
Bulgarian	0.0425	0.0077	0.0432	0.0082	****	0.9585	0.9352	0.9923
British	0.0006	0.0504	0.0012	0.0508	0.0424	****	0.9756	0.9507
Finnish	0.0247	0.0751	0.0250	0.0755	0.0670	0.0247	****	0.9276
Greek	0.0507	0.0006	0.0511	0.0008	0.0078	0.0506	0.0752	****

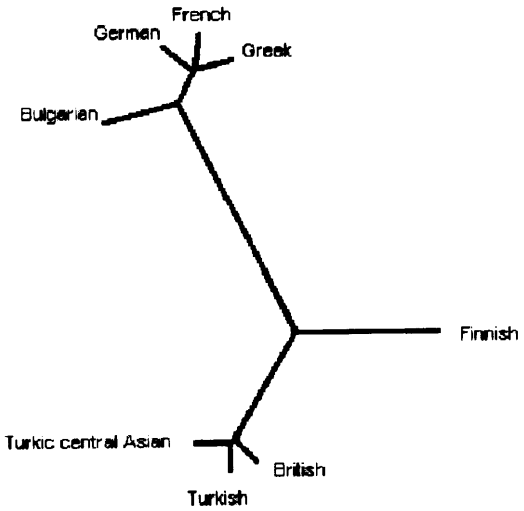

Figure 4. Neigbour-joining tree of European, Turkic central Asian and Turkish (Anatolian) populations constructed from HVS I sequences.

in this study (0.0155) is smaller than that found in central Asia, and higher than the figures reported for Europe. Nucleotide diversity in central Asia, ranges from 0.0164 in Uighurs to 0.0185 in the Kazakhs. The nucleotide diversities observed in several European populations are generally less than those found in central Asia, ranging from 0.0082 in Basques to 0.140 in Tuscany (Francalacci *et al*. 1996).

Our study provides comprehensive data concerning the genetic structure of Turkey which is located in an area known to be the gate between Asia and Europe. Genetic structure of the mtDNAs in the Turkish population bears similarities to Turkic central Asian populations. The nucleotide diversity value and the presence of common polymorphisms with both European and Asian populations provide further support for the intermediate location of Anatolia between Europe and Asia.

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Author's corrections

1. Owing to technical problems during preparation of figure 2, some nucleotides and their positions either are not correct or do not appear in the printed figure (page 41). We apologize for the unintentional errors and emphasize that these do not alter the haplogroups, neighbour-joining tree, frequencies, or the conclusions drawn in the original published study. The revised figure 2, without the neighbour-joining tree, follows this statement. Data in the revised figure 2 are referable to table 3.

2. In the legend to figure 3 (page 45), parts 3c and 3e are incorrectly identified. The correct labelling should be vice versa; 3c refers to the central part of Anatolia and 3e refers to the eastern part of Anatolia.

3. Because of the mislabelling in legend to figure 3:

(i) The second and following sentences of 'Pairwise differences' section in Results (page 42) should read: For segments I and II, samples from the eastern and northern Anatolia present peaks at 3 and 4 differences, with means of 4.56 ± 0.590 and 4.42 ± 0.556 differences, respectively. The samples from central Anatolia region had five peaks at 1, 2, 3, 5 and 6 with a mean of 4.29 ± 0.760 differences. The samples from western Anatolia region show two peaks at 2 and 4 with a mean of 3.62 ± 0.850 differences, ….

(ii) The first sentence of para 5 of Discussion (page 44, right column, last para) should read: The pairwise difference for segment I and II showed a bell-shaped distribution in northern, southern and eastern Anatolia (figures 3a,d,e, respectively), and an irregular, multimodal distribution in western and central Anatolia (figures 3b,c, respectively).

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The revised part of figure 2 is on the next page