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HUMAN GENETICS

Analysis of the Allele Frequencies of Seven Y-Chromosome Microsatellite Loci in Three Tuvinian Populations

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Abstract—The allele frequency distribution of seven microsatellite loci of the nonrecombining region of the Y chromosome (Y-STRs) was analyzed in three geographically distant indigenous populations of the Tuva Republic. The populations did not differ in allele frequency distribution of the seven Y-STRs. The Y-chromosome microsatellite loci in Tuvinians showed a high diversity ($H = 0.575$) that was nearly identical in all three populations. The genetic distance D_{dm} between the three populations was low, suggesting no subdivision of the modern male population of Tuva. Estimates of the period of linear changes in D_{dm} showed that Y-chromosome microsatellites can be used to reconstruct evolutionary events dating back no more than 40 000–50 000 years. The problems of human population phylogeny are discussed on the basis of data on Y-chromosome STRs.

INTRODUCTION

Analysis of the Y-chromosome lines is among the most topical problems in human population and evolutionary genetics [1, 2]. Until recently, the Y chromosome was believed to be low-polymorphic. However, studies of the last several years have revealed that this smallest human chromosome is comparable with autosomes in genetic variation [3, 4]. Information on more than 400 genetic markers of the Y chromosome is now available from the Genome Database (GDB), including data on single-nucleotide polymorphisms (SNPs) and short tandem repeats (STRs), or microsatellites.

In this work, we analyzed the allele frequency distribution of seven microsatellite loci of the nonrecombining region of the Y chromosome in three geographically distant and ethnically heterogeneous Tuvinian populations. Tuvinians (235 000 people [5]) are the indigenous population of the Tuva Republic, belonging to the Altaic language family of the Turkic group [6, 7]. The formation of the modern Tuvinian ethnos is based on several components, including Turkic, Mongol, Ket-speaking, Samodian-speaking, and Indo-European ethnic influences [8–10]. Ethnographic and anthropological data suggest heterogeneity of the ancient and modern populations of the Tuva region [8–10]. Analysis of genetic polymorphisms, including variation in proteins [11–13], mitochondrial DNA [13, 14], and several nuclear genes [15], has confirmed the appreciable genetic differentiation of the modern indigenous population of the Tuva Republic. The objectives of this work were to study the allele frequency distributions of seven Y-chromosome STRs in populations from the western, eastern, and southeastern regions of the republic; to estimate the genetic diversity and differentiation of these populations; and to analyze their place on the phylogenetic tree of modern human populations.

MATERIALS AND METHODS

Characterization of the populations studied. The material was collected in three geographically distant Tuvinian populations: the villages Kungurtug ($N = 47$), Toora-Khem ($N = 30$), and Teeli ($N = 36$) (Fig. 1). The village Kungurtug (Shinaan raion) is in the southeastern region of the Tuva Republic, which borders Mongolia. The Kungurtug population is geographically isolated and includes an appreciable proportion of descendants from Mongol families. The village Toora-Khem (administrative center of the Todzhin raion) is in a rather inaccessible highland region. The population of this region of the Tuva Republic (Todzhinians) is considered as a separate ethnic group in the Tuvinian ethnos. The village Teeli (administrative center of the Bai-Tagin raion) is in the western region, which has produced industries and developed communication with other regions of the Tuva Republic. The material was collected during the expeditions of the Institute of Medical Genetics from 1993 to 1997 [13]. Only ethnic Tuvinians unrelated in the male line were analyzed.

Experimental procedures. Genomic DNA was isolated from peripheral blood lymphocytes by the standard method. PCR was used to amplify seven microsatellite loci of the nonrecombining region of the Y chromosome: *DYS389I, DYS389II, DYS390, DYS 391,*

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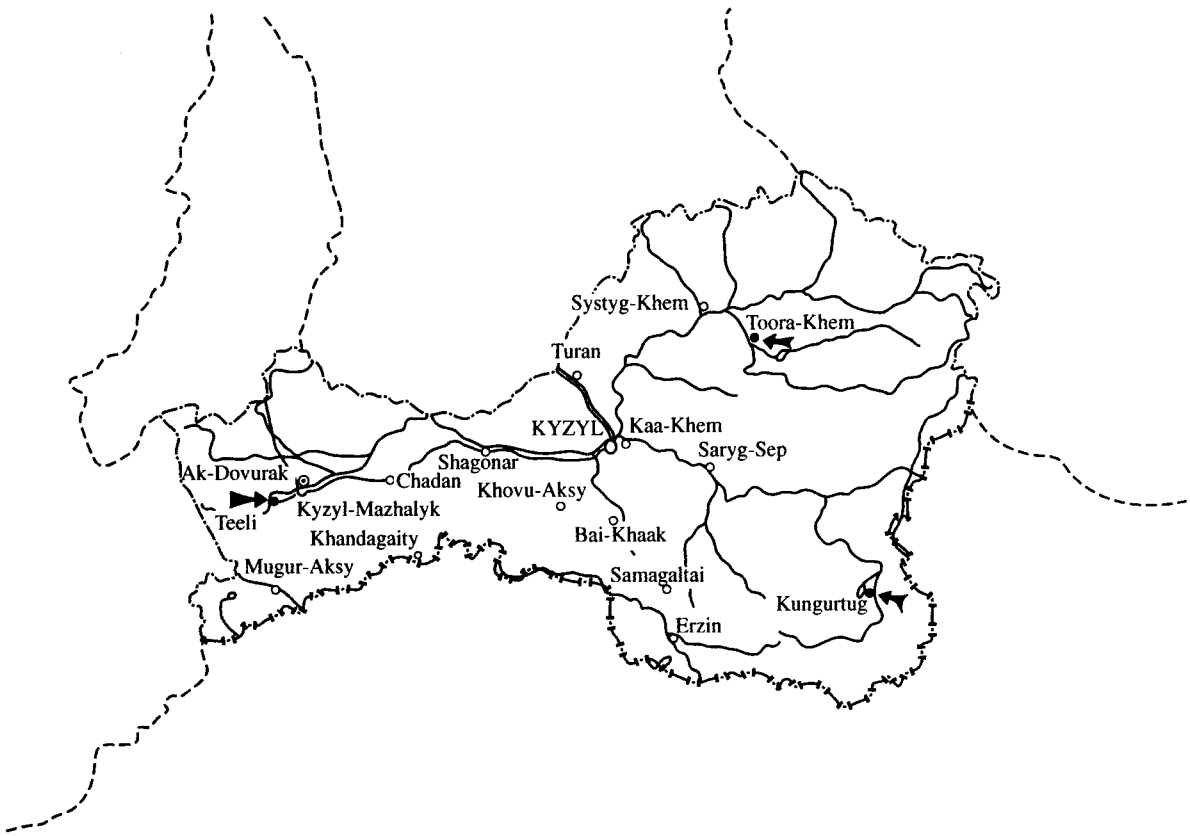

Fig. 1. Geographic location of the three populations studied (indicated with arrows) in the Tuva Republic.

DYS392, *DYS393*, and *DYS394* (*DYS19*). All but one locus included tetranucleotide repeats; the *DYS392* locus included a trinucleotide repeat. Primers and amplification conditions were as described earlier [16–18]. For each locus, direct primers were fluorescence-labeled at the 5'-end; the label was 4,7,2',7'-tetrachloro-6-carboxyfluoresceine (TET) for *DYS389I/II* and *DYS394*, 6-carbosyfluoresceine (FAM) for *DYS392* and *DYS393*, and 4,7,2',4',5',7'-hexachloro-6-carboxy-fluoresceine (HEX) for *DYS390* and *DYS391*. The primers were synthesized and labeled by the Perkin–Elmer Oligo Factory (Germany).

The products amplified from individual loci were pooled and separated by capillary gel electrophoresis in a Perkin–Elmer ABI Prism 310 genetic analyzer, with GeneScan-500/TAMRA molecular weight markers. The fragment length was estimated and genotypes were determined with the GeneScan Analysis package (Perkin–Elmer).

Allele classification. Alleles were designated according to the repeat number within the corresponding STR [16, 17, 19]. The primers for the *DYS389* locus allowed simultaneous amplification of two microsatellite repeats, *DYS389II* (*DYS389A*) and *DYS389I* (*DYS389B*); the products were of 353–385 and 239–263 bp, respectively [19]. The repeat number in the *DYS389II* locus was determined from the difference between the lengths of the larger fragment and the fragment amplified from *DYS389I*.

Statistical analysis. The allele frequencies were determined by the standard method. Gene diversity H was calculated as $H = 1 - \sum p_i^2$, where p_i is the frequency of allele i. This parameter is equivalent to theoretically expected heterozygosity at autosomal loci and characterizes the genetic diversity of a population [20].

To estimate the genetic distance between populations from the total data on all loci, we used genetic distance $D_{dm}(\delta\mu^2)$ based on the variance of repeat numbers [21]. Recent works showed that D_{dm}, rather than other parameters used to characterize the genetic distance from data on microsatellites, allowed construction of a phylogenetic tree with correct topology and branch length [22]. A matrix of genetic distance between populations was obtained using the MCROSAT program [23], with 500 bootstrap iterations. Based on this matrix, a dendrogram of genetic relationships between populations was constructed with the PHYLIP 3.5 package [24] utilizing the neighbor-joining procedure [25]. A consensus tree was obtained with 1000 bootstrap iterations of the initial data. The dendrogram was displayed with the TREEVIEW program [26].

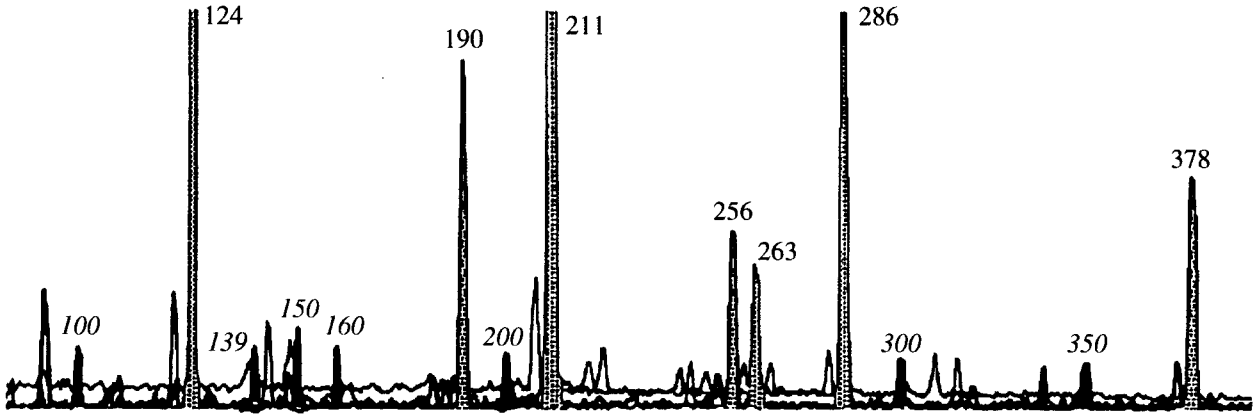

Fig. 2. Electrophoretic separation of DNA fragments PCR-amplified from DNA of individual TKh10 and pooled. Fragment size (bp) is indicated. The fragment 124 corresponds to the locus *DYS393* (allele 13); fragment 190, to *DYS394* (allele 14); fragment 211, to *DYS390* (allele 23); fragment 256, to *DYS389I* (allele 11); fragment 263, to *DYS392* (allele 16); fragment 286, to *DYS391* (allele 11); and fragment 378, to *DYS389I/II*. The fragment size of the GeneScan-500/TAMRA molecular weight markers is in italics.

RESULTS AND DISCUSSION

Allele Frequency Distribution and Genetic Diversity of the Populations

An example of electrophoretic separation of fragments amplified from the seven Y-chromosome microsatellites is shown in Fig. 2. The allele frequencies of the three Tuvinian populations are summarized in Table 1.

All but one Y-STR showed a unimodal frequency distribution, with one allele being the most common and the frequency of the others decreasing as the difference in repeat number compared with that of the most common allele increased. This distribution pattern was consistent with a model of step-by-step mutations (i.e., each mutation increased or decreased a repeat array by one unit) and was reported earlier for other populations [17, 27–30]. The *DYS392* locus displayed the bimodal allele frequency distribution: allele 14 was the most common, allele 11 occurred at a slightly lower frequency, and the intermediate alleles 12 and 13 were rare. This distribution pattern has also been observed in other populations [17, 27–30].

Pairwise comparisons did not reveal a significant difference in allele frequency between the three Tuvinian populations, although the most frequent *DYS391* allele was allele 10 in the Kungurtug population and allele 11 in the two others. The genetic diversity of the three Tuvinian populations is characterized in Table 2. The *DYS394* (H = 0.743) and *DYS389II* alleles (H = 0.705) proved to be the most polymorphic in Tuvinians. The *DYS393* locus showed the lowest polymorphism (H = 0.372). The three Tuvinian populations did not differ in gene diversity averaged over all seven Y-chromosome microsatellites. However, as inferred from the parameter H and the average allele number m of the same seven Y-STRs, gene diversity in Tuvinians was significantly higher than in Catalonians and Basques (m = 4.3, H = 0.465) [27].

Phylogeny of Populations

Since the effective size of the Y-chromosome pool is low, a high interpopulation variation is characteristic of Y-chromosome markers. Hence, the Y-chromosome STRs are a convenient tool for studying the phylogenetic relationships of modern human populations. Based on our results and published data [17, 27, 28, 30] on the seven Y-STRs, we estimated the genetic distance between populations from various races and geographic regions. Genetic distance was computed as D_{dm}, as this parameter had been specifically designed for microsatellites with step-by-step mutations [21]. The distance D_{dm} was –0.48 between the Teeli and Toora-Khem populations, –0.005 between the Kungurtug and Teeli populations, and –0.009 between the Kungurtug and Toora-Khem populations. Thus, the western Tuvinian population (Teeli) and Todzhinians from Toora-Khem were more closely related to each other than to the southeastern Tuvinian population (Kungurtug).

A matrix of genetic distance between 27 populations, including the 3 Tuvinian populations and 24 populations described elsewhere, was constructed on the basis of 500 bootstrap iterations of the allele frequency data. To characterize the relationships of the populations, a consensus dendrogram was obtained using 1000 iterations of the matrix of genetic distances (Fig. 3). The three Tuvinian populations formed a separate cluster on the dendrogram. As expected from the D_{dm} values, the Teeli and Toora-Khem populations formed a subcluster within the cluster of all Tuvinian populations. Interestingly, our dendrogram suggested a significant distance between Tuvinians and Mongols, though the contribution of the Mongol gene pool to that of Tuvinians had been well documented.

The Tuvinian populations were clustered together with the European populations and the indigenous American population (Amerindians). Another large cluster included populations from Oceania, a single

Table 1. Allele frequencies of the seven Y-chromosome microsatellite loci in the three Tuvinian populations

Locus	Allele	Kungurtug		Teeli		Toora-Khem		Total	
		N	%	*N*	%	*N*	%	*N*	%
DYS389I	8			1	2.9			1	0.9
	9	5	10.6	2	5.9	3	10.0	10	9.0
	10	31	66.0	18	52.9	21	70.0	70	63.1
	11	11	23.4	13	38.2	5	16.7	29	26.1
	12					1	3.3	1	0.9
	Total	47	100.0	34	100.0	30	100.0	111	100.0
DYS389II	15					1	3.3	1	0.9
	16	1	2.1	2	5.9			3	2.7
	17	5	10.6	2	5.9	1	3.3	8	7.2
	18	20	42.6	18	52.9	10	33.3	48	43.2
	19	8	17.0	7	20.6	13	43.3	28	25.2
	20	13	27.7	4	11.8	5	16.7	22	19.8
	21			1	2.9			1	0.9
	Total	47	100.0	34	100.0	30	100.0	111	100.0
DYS390	19	1	2.1					1	0.9
	23	30	63.8	23	67.6	22	73.3	75	67.6
	24	11	23.4	8	23.5	3	10.0	22	19.8
	25	5	10.6	3	8.8	4	13.3	12	10.8
	26					1	3.3	1	0.9
	Total	47	100.0	34	100.0	30	100.0	111	100.0
DYS391	9	2	9.5	5	13.9	1	3.4	8	9.3
	10	12	57.1	10	27.8	12	41.4	34	39.5
	11	7	33.3	21	58.3	16	52.2	44	51.2
	Total	21	100.0	36	100.0	29	100.0	86	100.0
DYS392	11	15	31.9	10	29.4	6	20.0	31	27.9
	12	1	2.1	1	2.9	5	16.7	7	6.3
	13	1	2.1	1	2.9	1	3.3	3	2.7
	14	28	59.6	20	58.8	16	53.3	64	57.7
	15	2	4.3	1	2.9			3	2.7
	16			1	2.9	2	6.7	3	2.7
	Total	47	100.0	34	100.0	30	100.0	111	100.0
DYS393	11	2	4.3	2	5.9	3	10.0	7	6.3
	12	36	76.6	28	82.3	22	73.3	86	77.5
	13	9	19.1	4	11.8	4	13.3	17	15.3
	14					1	3.3	1	0.9
	Total	47	100.0	34	100.0	30	100.0	111	100.0
DYS394	12	1	2.1					1	0.9
	13	12	25.5	3	8.8	7	23.3	22	19.8
	14	6	12.8	8	23.5	5	16.7	19	17.1
	15	17	36.2	15	44.1	9	30.0	41	36.9
	16	10	21.3	8	23.5	7	23.3	25	22.5
	17	1	2.1			2	6.7	3	2.7
	Total	47	100.0	34	100.0	30	100.0	111	100.0

African population (Pygmies), and two of three Asian populations (Chinese and Mongols).

This phylogenetic tree markedly differed from those constructed from data on classical (protein) markers [31], mitochondrial DNA [32, 33], autosome microsatellites [34–36], and autosome diallelic markers [31, 34, 37]. The difference can be explained by (1) specific properties of the data analyzed, (2) the genetic nature of Y-chromosome microsatellites, and (3) specific population genetic processes in the male gene pool.

The first explanation concerns the populations that were analyzed. The proportions of populations from various racial and ethnic groups and from various regions differ from the proportions they comprise in the total human gene pool. Thus, only a few populations from Africa and Asia were studied, whereas populations from other regions (Europe, the New World) comprised a far greater proportion in the data analyzed than in the world gene pool. In addition, the Y-STRs used to construct the dendrogram are closely linked, rather than independent, markers. Possibly, another tree would be obtained with haplotype frequencies. However, we could find no data on haplotype frequency distributions in most of the above populations.

The second explanation concerns the genetic nature of Y-chromosome microsatellites. First, as STRs display a high frequency of mutations, the frequency of recurrent mutations can be expected to be similarly high. Consequently, the same alleles and haplotypes detected in individual populations may suggest similar but independent mutations rather than any relatedness of the populations. Second, with the Y-STR mutation rate most reliably estimated at 1.2×10^{-3} [28], the distance D_{dm} computed from the data on the seven Y-STRs in the three Tuvinian populations changed linearly for 1766 generations or, assuming the mean generation time to be 25 years, for approximately 44 000 years (Table 3). This was the period of linear changes averaged over all seven loci. However, this period markedly varied with microsatellites, being minimal (566 generations) for the *DYS393* locus and maximal (3300 generations) for the *DYS390* locus. This was consistent with the data reported by de Knijf *et al.* [17], who obtained similar estimates for the period of linear changes in D_{dm} with the same seven Y-chromosome microsatellites. Thus, when analyzing evolution of human populations, the Y-chromosome STRs can be used to reconstruct only evolutionary events dating back no more than 40 000–50 000 years. In comparison, evolutionary changes in autosome STRs have been assumed to remain linear for 500 000–600 000 years [21], which is first and foremost explained by a low mutation rate.

Finally, the dendrogram based on the Y-chromosome microsatellites could reflect population processes (e.g., gene drift and migration) that specifically affect the male gene pool. Thus, as compared with autosome or mtDNA markers, the Y-chromosome loci display higher random variation in frequency (genetic drift). As a result, their interpopulation variation makes a greater contribution to the total gene diversity, and the geographical clustering of Y-chromosome variants is higher. In addition, a tree constructed from data on Y-chromosome markers, but not a tree based on autosome or mtDNA markers, may characterize historical migrations of large male populations (e.g., caused by campaigns of war or colonization).

Thus, the analysis of the allele frequency distribution of the seven microsatellite loci from the nonrecombining region of the Y chromosome did not reveal any significant difference between the three geographically distant Tuvinian populations. The similarity of their Y-chromosome pools was inconsistent with the appreciable linguistic and anthropological differences between populations from individual regions of the Tuva Repub-

Table 2. Gene diversity of the three Tuvinian populations estimated from data on the seven Y-chromosome microsatellites

Locus	Number of alleles	Population			Total	Average per population
		Kungurtug	Teeli	Toora-Khem		
DYS389I	5	0.498	0.569	0.471	0.525	0.513
DYS389II	7	0.701	0.657	0.672	0.705	0.677
DYS390	5	0.527	0.480	0.434	0.508	0.480
DYS391	3	0.591	0.564	0.554	0.592	0.570
DYS392	6	0.540	0.564	0.642	0.583	0.582
DYS393	4	0.375	0.305	0.434	0.372	0.371
DYS394	6	0.741	0.687	0.769	0.743	0.732
Average per locus	5.1	0.568	0.547	0.568	0.575	0.561

Table 3. Period of linear changes in genetic distance D_{dm} estimated from the variance of repeat number of the seven Y-STRs in the three Tuvinian populations

Locus	Repeat number			Period of D_{dm} linear changes	
	min	max	difference	generations	years
DYS389I	8	12	4	1042	26000
DYS389II	15	21	6	2431	61000
DYS390	19	26	7	3333	83000
DYS391	9	11	2	1667	42000
DYS392	11	16	5	1667	42000
DYS393	11	14	3	556	14000
DYS394	12	17	5	1667	42000
Mean				1766	44000

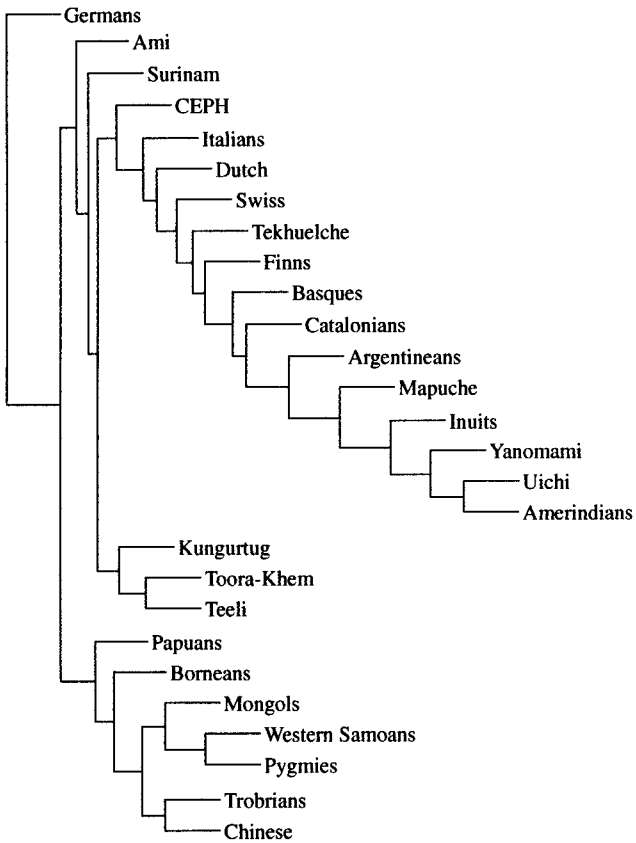

Fig. 3. Dendrogram of genetic relationships between populations constructed from data on the six Y-STRs. In addition to the allele frequencies in the three Tuvinian populations studied in this work, we used data on Basques, Catalonians [27], Finns [30], Amerindians, CEPH [28], and other populations [17]. The populations were from various regions and racial groups: Africa (Pygmies), Oceania (Papuans, Borneans, Western Samoans, and Trobrians), Asia (Chinese, Mongols, Ami, Tuvinians), America (Surinam, Tekhuelche, Mapuche, Yanomami, Uichi, Inuits, Amerindians), the Caucasoid race (Germans, CEPH, Italians, Dutch, Swiss, Finns, Basques, Catalonians, Argentineans).

lic and with high genetic differentiation of Tuvinians with respect to protein and mtDNA polymorphisms. The dendrogram of phylogenetic relationships between modern human populations showed that the male gene pool of Tuvinians was separated from that of the modern European populations and even from the male gene pool of the groups that had recently contributed to the formation of modern Tuvinians. Our data on the genetic relationships of populations confirmed that a genetic tree based on Y-chromosome loci might topologically differ from trees based on autosome or mitochondrial genes and polymorphisms. Estimation of the period of linear changes in genetic distance confirmed that, compared with autosome microsatellites, Y-chromosome STRs can be used to reconstruct much more recent evolutionary events (of the last 40 000–50 000 years).

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