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Genetic Differentiation of the Tuva Population with Respect to the *Alu* Insertions

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Abstract—Polymorphism of three rural populations of the Tuva Republic was examined using a set of five autosomal *Alu* insertions at the *ACE, PLAT, PV92, APOA1,* and *F13B* loci. The allele frequency distribution patterns revealed in Tuvinians were typical to Mongoloid populations of Asia and were characterized by relatively high frequency of the *Alu*-repeat insertion at the *PV92* and *F13B* loci along with relatively low insertion frequency at the *APOA1* locus. With respect to the test systems used, Tuvinian populations examined displayed high levels of genetic diversity. The mean expected heterozygosity values in the populations of Kugurtug, Toora-Khem, and Teeli were 0.433, 0.407, and 0.437, respectively. The level of genetic diversity in the pooled Tuvinian sample was 0.432. The coefficient of genetic differentiation in the three populations studied was 1.45 pointing to relatively low level of genetic subdivision of the indigenous Tuvinian populations. However, estimates of genetic differentiation of the Tuvinian gene pool made by use of the *Alu*-repeat system were higher compared to those performed using classical protein systems, mtDNA, or Y- chromosomal haplotypes. Even though Tuvinian populations were characterized by common gene pool, some features specific to Western Tuvinian population could be distinguished. These features could be associated with higher contribution of the Caucasian component to the gene pool of this population. Phylogenetic analysis demonstrated close genetic relationships between the Tuvinian and Altaic ethnic populations.

INTRODUCTION

Tuvinian populations have become the subject of extensive genetic, demographic, population and evolutionary genetic studies [1–12]. The reason for such interest lies in specific ethnogeny of Tuvinian populations, as well in the problems of the peopling and evolution of human populations in Eurasia and the New World. Tuvianians represent one of the largest indigenous population (the population number is 265 000) and belong to the Turkic group of the Altaic linguistic family. The appearance of the modern humans on the territory of Tuva dates back to late Paleolith. During the Neolithic and the Bronze Age this territory was inhabited by Caucasian tribes, which migrated there from the steppes of Western Eurasia. The history of the Tuvinian ethnogeny starts in the so-called Scythian time (2700-2300 years ago). Then, during the "Huno-Sarmatian time" (2nd century B.C.–5th century A.D.) intense Mongolization and Turkicization of the population of the Minusinskii basin occurred. In the subsequent periods the Uiguric, Kyrghyz, and Mongolian tribes made a considerable contribution to the Tuvinian ethnogeny [13–15].

The data of anthropological, ethnographic, and linguistic investigations point to remarkable differences between territorial groups of Tuvinians. Specifically, on the territory of the Tuva Republic three anthropological types have been distinguished: Mongoloid type, characteristic of Southern Tuvinian groups; an anthropological type with low expression of the Mongoloid component, characteristic of the Western Tuvinian population; and an independent group of Todja Tuvinians, inhabiting the northwestern part of the Republic, which is sometimes attributed to the Baikalic anthropological type [16, 17]. Similar territorial differentiation is also reported by linguists, who distinguish several dialects of the Tuvinian language [18, 19].

Genetic investigations of Tuvinian populations started in the mid-1960s, when a number of Tuvinian populations were tested for a number of immunological marker systems (ABO, Rhesus, P. Lewis, and some others) [20, 21]. Further studies focused on the analysis of the polymorphism of Tuvinian populations with respect to immunological and biochemical markers were carried out by several research groups [16, 22]. Most of these works were aimed at elucidation of genetic relationships between Tuvinians and other Siberian ethnic groups. Moreover, the investigations were carried out using isolated populations mostly inhabiting the central region of the Tuva Republic. In recent years these surveys were continued in the studies concerning DNA polymorphisms at different genetic loci.

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ences, complex investigation of the genetic diversity of the Tuvinian populations differing by anthropological and genetic characters [23] and representing different regions of the Tuva Republic, is in progress. A set of different marker systems, including those, detecting classical immunological and biochemical polymorphisms [23], as well as DNA marker systems, represented by mtDNA lineages [4– 6], Y-chromosomal [8–10], and highly polymorphic autosomal markers [11], are used. Genetic demographic approaches are also employed [1–3].

To characterize genetic diversity and differentiation of the three Tuvinian populations, as well as to analyze genetic relationships between Tuvianians and other ethnic groups, a set of five autosomal *Alu* insertion polymorphisms was used. The *Alu* elements are a family of most common short interspersed repeated DNA sequences (SINEs) in humans with about 500 000 copies per genome [24]. Some of the *Alu* elements are transcriptionally active and can be transposed to the new genome loci via retroposition [25, 26]. *Alu* elements belong to the ancient DNA sequences (of the age exceeding 100 Myr) and are found in the genomes of many species. The *7SL* RNA gene is thought to be the evolutionary precursor of *Alu* repeats [27]. Some families of the *Alu* elements (Ya, Yb, and Sb) are considered to be human-specific, since retroposition of their master-copy have occurred in recent times. Most of these *Alu* elements are monomorphic; however, some loci, where insertions of the *Alu* repeats occurred as early as during ethnic radiation and settling of the modern humans, appear to be polymorphic in respect to the presence/absence of the *Alu* repeat copy.

Some features of the polymorphic *Alu* loci make them convenient genetic markers for population genetic studies. These features include high stability of the *Alu* element, low level of *de novo* insertions, and absence of the mechanism regulating excision of the *Alu* repeat from a particular locus. These characteristics allow to consider the insertion of an *Alu* repeat in a single locus as an independent event that happens only once. Furthermore, the nature of the *Alu* element transpositions permits unambiguous determination of the initial (absence of the *Alu* repeat in the given locus) and terminal (*Alu* insertion) allelic state of the locus. At present, polymorphic *Alu* repeats along with other genetic marker systems are widely used to estimate genetic diversity of human populations [28–30]. This study presents the first description of the gene pools of three Tuvinian populations using a set of five polymorphic *Alu* insertions located at the *PV92* locus, as well as at the genes for angiotensin-converting enzyme (*ACE*), beta-subunit of the blood clotting factor VIII *F13B*), apolipoprotein A1 (*APOA1*), and plasminogen activator (*PLAT*). This analysis was undertaken with the purpose of characterization the genetic diversity and degree of genetic differentiation of these populations, and also for determination of their position in the general phylogenetic pattern of modern humans.

MATERIALS AND METHODS

Characteristics of the populations studied. Three Tuvinian population samples from the settlements of Kungurtug ($N = 165$), Teeli ($N = 129$), and Toora-Khem ($N = 114$) were examined. The settlement of Kungurtug (Shinaanskii raion) is located in the southeast of the Republic, close to the Mongolian border. The Kungurtug population is characterized by geographical isolation and a high proportion of the descendants of the Mongolian tribes. The settlement of Toora-Khem (Todjinskii raion) is located in the difficult to access mountain region east of the Tuva Republic. The population of the settlement is represented by an isolated ethnographic group of Todja Tuvinians. The settlement of Teeli (administrative center of the Bai-Taiginskii raion) is located in the industrial western part of the Republic. It has good transport communications with the other parts of the Republic. The samples were collected during expeditions undertaken between 1993 and 1997 [23]. Only unrelated individuals with confirmed attribution to Tuvinian ethnic group participated in the study. Comprehensive genetic and demographic characteristics of the populations studied are given in our previous works [1–3, 23].

Experimental procedures. DNA was extracted from peripheral blood lymphocytes according to a standard technique. Genotyping was carried out by means of PCR followed by electrophoresis in 2% agarose gel. Visualization of the gels and documentation of the results were conducted using VIDEO STUDIO, version 1.0 (Ulead Systems); and VIDEO PACKER PLUS, version 1.2p (Aura Vision & VIC Hi Tech) software programs. The allele nomenclature used implied that *Alu+* is the presence of the *Alu* insertion in particular locus, and *Alu–* is the lack of insertion.

Statistical evaluation. The allele frequencies, conformity of the genotype distribution to Hardy–Weinberg equilibrium, the observed and expected heterozygosity, as well as their errors were calculated according to standard methods [31]. Genetic distances between the populations and the coefficient of genetic differentiation, G_{ST}, were calculated according to Nei [32]. The population phylogenetic tree was constructed according to the method of Saitou and Nei [33] by means of the PHYLIP software package [34] and using 1000 bootstrap iterations.

RESULTS AND DISCUSSION

Allele Frequencies and Genetic Diversity of Tuvinian Populations

The allele frequencies, genotype distribution and its conformity to Hardy–Weinberg proportions, as well as the expected and observed heterozygosity at each locus for three Tuvinian populations tested are presented in Table 1. In general, the allele frequency distribution patterns revealed in Tuvinians were typical to Mongoloid populations of Asia [28, 29] and were characterized

Table 1. Distribution of genotypes, allele frequencies, and genetic diversity indices in the populations studied

Population	*N*	Genotypes			The *Alu* (*Alu*+) frequency	χ^2	H_O	H_e
		+/+	+/–	–/–				
					ACE			
Kungurtug	165	40	89	36	0.5121 ± 0.0275	1.04	0.539	0.500
Toora-Khem	129	38	65	26	0.5465 ± 0.0310	0.03	0.504	0.496
Teeli	113	26	35	52	0.3850 ± 0.0324	13.5*	0.305	0.473
					PLAT			
Kungurtug	141	17	78	46	0.3972 ± 0.0291	3.39	0.553	0.479
Toora-Khem	127	14	36	27	0.4156 ± 0.0397	0.11	0.467	0.486
Teeli	96	15	48	33	0.4063 ± 0.0354	0.13	0.500	0.482
					PV92			
Kungurtug	97	49	35	13	0.6856 ± 0.0333	2.58	0.361	0.431
Toora-Khem	85	39	41	5	0.7000 ± 0.0351	1.87	0.482	0.420
Teeli	96	42	34	20	0.6146 ± 0.0351	6.12***	0.354	0.474
					APOA1			
Kungurtug	95	48	34	13	0.6842 ± 0.0337	2.80	0.358	0.432
Toora-Khem	80	38	35	7	0.6938 ± 0.0364	0.07	0.437	0.425
Teeli	93	57	30	6	0.7742 ± 0.0307	0.56	0.323	0.350
					F13B			
Kungurtug	88	60	20	8	0.7955 ± 0.0304	8.00**	0.227	0.325
Toora-Khem	80	64	13	3	0.8813 ± 0.0256	3.99***	0.162	0.209
Teeli	95	49	38	8	0.7158 ± 0.0327	0.03	0.400	0.407

Note: χ^2, the test for conformity to Hardy–Weinberg equilibrium.
* $P < 0.001$.
** $P < 0.01$.
*** $P < 0.05$.

by relatively high frequency of the *Alu*- repeat insertion at the *PV92* and *F13B* loci along with relatively low insertion frequency at the *APOA1* locus. The data on these particular loci permit precise distinguishing between Caucasian and Mongoloid populations. The frequency of the *Alu* element insertion at the *PV92* locus in Caucasians constitutes from 0.15 to 0.30, while in Mongoloids it varies from 0.53 to 0.70. The frequency of the *Alu* element insertion at the *F13B* locus in the Asian Mongoloids varies from 0.71 to 0.85, while Caucasian populations are characterized by lower frequencies of the *Alu*+ allele (0.39 to 0.62). The *Alu* allele frequency distributions at the *APOA1* locus observed in Asia and Europe partly overlap with a tendency to a lower frequency of the *Alu*+ allele in Mongoloids. The frequency of the *Alu* insertion at the *PLAT* and the *ACE* locus, in particular, varies greatly both in Caucasians and in Mongoloids from Asia and the New World.

The Tuvinian populations examined were characterized by similar allele frequencies. Pairwise population comparisons by all the loci tested did not reveal statistically significant differences between the Tuvinians from Kungurtug and the Todja Tuvinians from Toora-Khem. However, there were slight differences between the Western Tuvinians (the settlement of Teeli) and the two other populations. By the insertion frequency at the *ACE* and the *F13B* loci the Teeli population was statistically significantly different from the Toora-Khem population (χ^2 = 12,5, df = 1, $P < 0.001$; and χ^2 = 14.412,5, df = 1, $P < 0.001$ respectively). Moreover, by the insertion frequency at the *ACE* locus the Teeli population was also statistically significantly different from the Kungurtug population (χ^2 = 8.7, df = 1, $P <$ 0.01). It is noteworthy that by the insertion frequencies at the loci mentioned and also by the insertion frequency at the *PV92* locus, where the differences between the Teeli population and the others were not so striking, Western Tuvinian population displayed some similarity with Caucasian populations, since in this population a shift of the *Alu* insertion frequencies towards the "Caucasian" type was observed. These findings are consistent with the data on higher expression of the Caucasian component in the anthropological type of this Tuvinian population [13–17].

The test for conformity of the genotype distribution to Hardy–Weinberg equilibrium revealed considerable

Table 2. Genetic differentiation of the Tuvinian populations

Locus	H_T	H_S	G_{ST}
ACE	0.500	0.490	0.020
PLAT	0.482	0.482	0.000
PV92	0.445	0.442	0.008
APOA1	0.405	0.402	0.006
F13B	0.329	0.314	0.045
Overall	0.432	0.426	0.014

deviation from the expected distributions at the *ACE* and the *PV92* loci in the Teeli population and at the *F13B* locus in the populations of Kungurtug and Toora-Hem (see Table 1). In all four cases the deviation resulted from the deficit of heterozygotes. This probably reflected the high level of inbreeding in these populations caused by their small sizes and the high degree of isolation. Previous studies showed that the populations analyzed were characterized by extremely high values of the inbreeding coefficient. The latter was calculated based on isonymic marriages, whose frequency in Tuva is an order of magnitude higher than in other indigenous Siberian populations examined so far [3, 23]. Note that the highest level of inbreeding was observed in the Bai-Taiga population (Teeli).

With respect to the five polymorphic systems tested, Tuvinian populations were characterized by high genetic diversity: the mean expected heterozygosity was 0.433 for Kungurtug; 0.407, for Toora-Khem; and 0.437, for Teeli. The level of genetic diversity in the pooled Tuvinian sample was 0.432.

Genetic Differentiation of Tuvinian Populations

The estimates of genetic subdivision of Tuvinian populations with respect to each polymorphic locus and to the set of the five *Alu* insertions are presented in Table 2. The value of genetic differentiation coefficient of the populations studied was 1.4%, pointing to relatively low level of genetic subdivision within indigenous Tuvinian populations. The data for individual loci show that the highest contribution to the between-population diversity is made by the differences in the frequencies of the *Alu* insertions at the *F13B* (G_{ST} = 4.5%) and the *ACE* (2.0%) loci. All Tuvinian populations examined displayed low differentiation with respect to the allele frequencies at the *PV92* and *APOA1* loci (G_{ST} ranges from 0.6 to 0.8%). Moreover, these populations appeared to be nearly monomorphic with respect to the allele frequencies at the *PLAT* locus.

In all, the level of subdivision of Tuvinian populations was considerably lower than the differentiation by the same loci within the populations of the Altaic linguistic family (G_{ST} = 3.6%) [35]. The subdivision of Tuvinian populations was also by an order of magnitude lower than the level of genetic differentiation of the worldwide population (G_{ST} = 12.8%), estimated based on the *Alu* insertion frequencies in the populations from different geographical regions [29].

It is noteworthy that compared to other genetic marker systems, the *Alu* elements provide maximal proportion of between-population differences to the total genetic diversity of Tuvinian populations. For instance, the three populations studied displayed very low level of genetic differentiation estimated with respect to classical immunological and biochemical loci (0.5%) [23]. Similar results were obtained by use of the mtDNA D-loop restriction haplotypes (G_{ST} = 0.6%) [23]. Moreover, these populations were monomorphic with respect to Y-chromosomal microsatellite haplotypes [9, 10].

Genetic Relationships between Tuvinians and Other Ethnic Populations of Siberia

To estimate the degree of genetic relatedness between Tuvinian populations and their relationships with other populations such as Mongoloids from the Altaic linguistic family, and some other ethnic groups, cluster analysis was used. For phylogenetic trees construction two databases were utilized. One of these included the information on the populations from Siberia and Central Asia analyzed earlier [35], while another in addition to our personal data contained the literature data on the frequencies of the *Alu* insertions in various World populations [28, 29]. To obtain most probable tree topology, a boostrap data rearrangement with generation of 1000 iterations of the initial data were carried out. Consensus dendrograms of genetic relationships were constructed by the neighbor-joining method using the PHYLIP software package [34]. The results are presented in Figs. 1 and 2. A hypothetical ancestral population, for which the frequencies of the *Alu* insertions in all five loci were taken as zero, served as outroot.

The topology of the first tree (Fig. 1) showed the closeness of the gene pools of the Toora-Khem and Kungurtug populations, as well as the closeness of the Teeli Tuvinians to the Altaic populations. At the same time, Tuvinian and Altaic populations formed a single cluster, which was clearly distanced from the Mongol-speaking Buryats, and Evenks, belonging to the Tunguso- Manchurian branch of the Altaic linguistic family, as well as from Mongoloid and Caucasian populations of Central Asia, and Slavic populations of Siberia. On the dendrogram reflecting genetic relationships between different world populations (Fig. 2) the Tuvinian—Altaic cluster looses its uniformity. On this dendrogram the Teeli Tuvinians and Altaic populations are located more closely to the Caucasian populations of Asia and Europe, while Tuvinian populations from the settlements of Toora-Khem and Kungurtug are placed in the cluster of Mongoloid populations of Asia and the New World. Thus, based on allele frequency distribu-

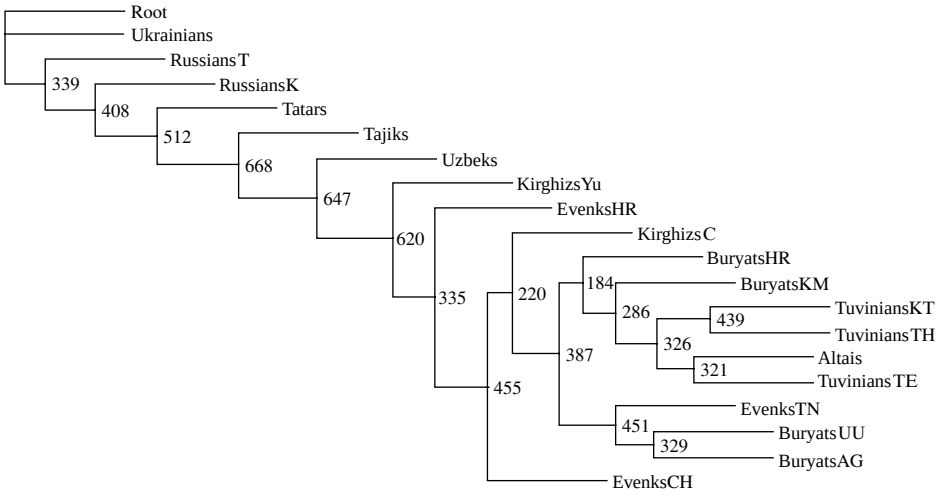

Fig. 1. Dendrogram of genetic relationships between the indigenous Siberian populations constructed by use of genetic distances calculated from the frequencies of five *Alu* insertions. The figures at the nodes are the numbers of bootstrap iterations, supporting the given branching. The designations of the populations are as follows: Root, external root (ancestral population); T, Tomsk; K, Kargala; S, South; N, North; CH, Chara; TN, Tungokochen; HR, Khuromsha; KM, Kurumkan; UU, Ulan-Ude; KT, Kungurtug; TH, Toora-Khem; TE, Teeli; AG, Aginskoe.

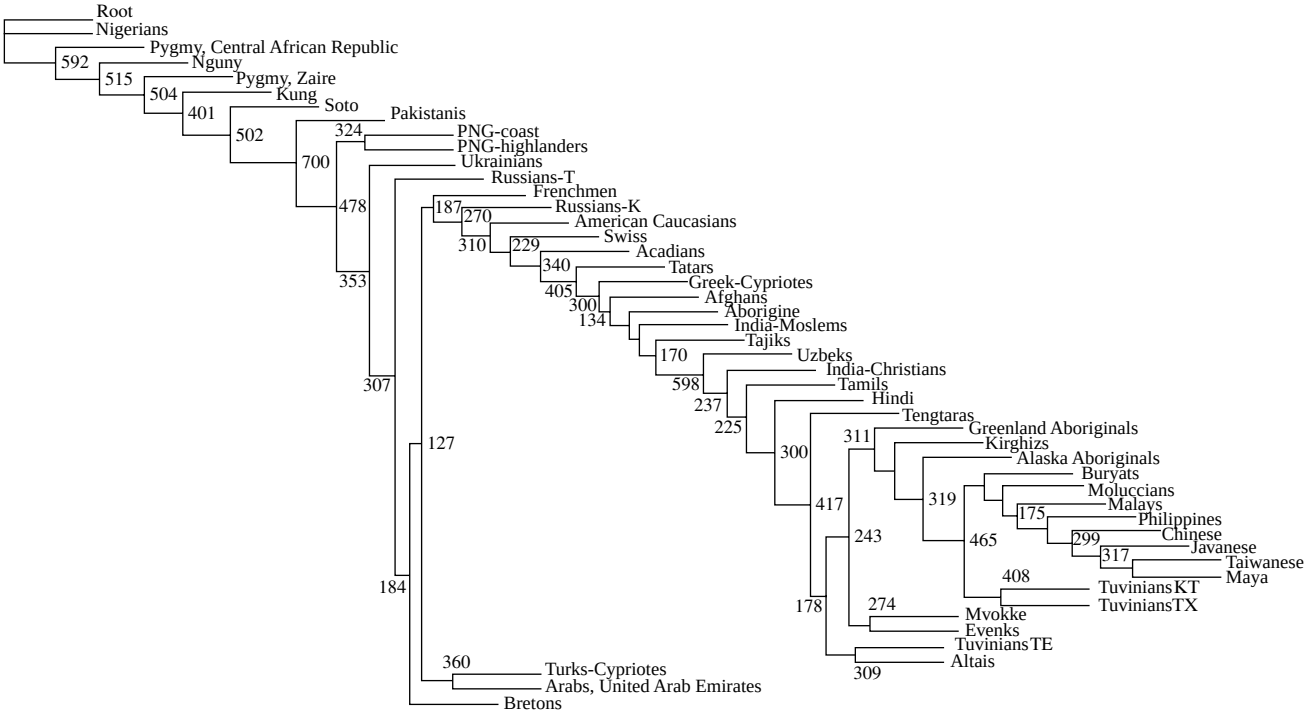

Fig. 2. Genetic relationships among the world populations. The abbreviations in the names of the populations are the same as in Fig. 1.

tions and phylogenetic analysis it can be suggested that somewhat isolated position of Western Tuvinians can be explained by higher proportion of Caucasian component in their autosomal gene pool. These findings are confirmed by anthropological data. Note, however, that here we speak only about autosomal part of the gene pool, since Western Tuvinians can not be distinguished from other Tuvinian populations neither by mtDNA, nor by Y-chromosomal haplotypes [9, 10, 23]. Moreover, Y-chromosomal haplotypes demonstrate equal to all Tuvinian populations contribution of the "ancient Caucasian" and the "ancient Turkic" components to the male gene pool of Tuvinian populations [10].

In summary, the data on autosomal *Alu* insertion polymorphism indicate that modern Tuvinians possess

common gene pool. On this background, however, some specific features of Western Tuvinians can be traced. These are probably associated with higher proportion of Caucasoid component in the gene pool of this population. Tuvinian populations displayed relatively low genetic subdivision with respect to polymorphic *Alu* repeat loci. The level of this subdivision, however, was higher than the degree of differentiation of Tuvinian populations revealed with respect to "classical" protein polymorphic systems, as well as paternal (Y chromosome) and maternal (mtDNA) lineages. The *Alu* insertion allele frequency distribution patterns revealed in Tuvinians were typical to Mongoloid populations of Asia. They also demonstrated close genetic relationships between Tuvinians and Altaic populations, probably, based on their common ethnogeny.

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