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HUMAN GENETICS

Genetic Variability and Structure of SNP Haplotypes in the *DMPK* Gene in Yakuts and Other Ethnic Groups of Northern Eurasia in Relation to Myotonic Dystrophy

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Abstract—The genetic variability of the *DMPK* locus has been studied in relation to six SNP markers (rs2070736, rs572634, rs1799894, rs527221, rs915915, and rs10415988) in Yakuts with myotonic dystrophy (MD) in the Yakut population and in populations of northern Eurasia. Significant differences were observed in the allele frequencies between patients and a population sample of Yakuts for three SNP loci (rs915915, rs1799894, and rs0415988) associated with a high chance of disease manifestation. The odds ratios (OR) of MD development in representatives of the Yakut population for these three loci were 2.59 (95% CI, p = 0,004), 4.99 (95% CI, $p = 0.000$), and 3.15 (95% CI, $p = 0.01$), respectively. Haplotype TTTCTC, which is associated with MD, and haplotype GTCCTT, which was observed only in Yakut MD patients (never in MD patients of non-Yakut origin), were revealed. A low level of variability in the locus of *DMRK* gene in Yakuts ($H_e = 0.283$) compared with other examined populations was noted. An analysis of pairwise genetic relationships between populations revealed their significant differentiation for all the examined loci. In addition, a low level of differentiation in territorial groups of Yakut populations ($F_{ST} = 0.79\%$), which was related to the high subdivision of the northern Eurasian population ($F_{ST} = 11.83\%$), was observed.

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INTRODUCTION

The results of genetic and epidemiological studies in the Sakha Republic (Yakutia) (SR (Ya)) revealed a high frequency of several forms of monogenic diseases, including myotonic dystrophy type I (MD) [1–8]. One mechanism of pathogenesis in a large number in human neuro-degenerative diseases, including MD, might be genomic instability, which occurs as a result of a three-nucleotide-repeat expansion. For the majority of diseases, population differ with respect to prevalence and spectrum and by the mutation frequencies in genes that determine their development. The rate of MD prevalence differs in various regions and ethnic groups. On average, the global frequency of cases of the disease for the examined pathology is 4–5 patients for every 100 thousand individuals in the population [9, 10]. The maximum frequency of MD was observed in Quebec (Canada): 189 cases per 100 thousand of residents [11]. In southeastern Asia the disease was observed extremely rarely; only one case in a Nigerian family was described in southern and central Africa. In the Yakut population, the MD frequency reaches a maximum in comparison with other Russian populations (21.3 per 100 thousand residents) [12]. This indicates the importance of disease studies for this region.

Myotonic dystrophy (MD, OMIM: 160900) is an autosomal dominant systemic disease characterized by wide variability in its manifestations, clinical polymorphism, and severity of the disease course. The major clinical manifestations are muscular weakness, cataract, cardiac arrhythmias, forehead alopecia, disturbance of glucose tolerance, and mental retardation. Studies of normal polymorphism in the myotonic dystrophy gene in SR (Ya) population indirectly provided evidence that the accumulation of this disease is governed by the founder effect. More than 500 SNPs have been described to date in the *DMPK* gene [13]. Studies of these SNPs were conducted in populations of Taiwan [14], Japan [15], Ethiopia [16], Southern Africa [17], Serbia [18], Iran [19], China [20], Thailand [21], Korea [22], and western Europe [23]. These data demonstrate significant interpopulation differences in the haplotype frequencies at the *DMPK* locus and an accumulation of distinct haplotypes in MD patients.

Table 1. Characteristics of the examined SNPs in the *DMPK* gene

Ref SNP ID (rs)	Polymorphism	Location in the gene	Nucleotide position	The enzyme used in PCR-RFLP
rs2070736	*G/T*	TEL from the intron	46286714	*Dra*III
rs572634	*G/T*	Intron 4	46282503	*Acc*B1I/*Hph*I
rs1799894	*C/T*	Intron 5	46281745	*Asp*LEI/*Hha*I
rs527221	*C/G*	Exon 10	46275976	*Bse*1I/*Bmp*I
rs915915	*G/T*	Intron 11	46274972	*Fnu*4HI
rs10415988	*D19S463*	15kbCEN	46246704	*Taq*I

The purpose of this study was to assess the genetic variability of the *DMPK* locus in Yakut MD patients and territorial samples of Yakut populations as compared with the northern Eurasian population, as well as to reveal a spectrum of the haplotypes associated with MD in Yakuts as compared with other world populations.

MATERIALS AND METHODS

DNA samples from 98 MD patients from 47 unrelated families and 50 of their phenotypically healthy relatives residing in SR(Ya) were used in the study. The patient data were obtained from the Republic Genetic Register of Hereditary and Congenital Pathology from Medical Genetic Service of the SR (Ya) Republic Hospital of the National Medical Center, as well as in the course of expeditions conducted in collaboration with the YaRC KMP Siberian Branch of the Russian Academy of Medical Sciences. The population sample of healthy subjects included native Yakuts residing in two ethnic geographic regions of the SR(Ya): Central (128 subjects) and Viluy (100 subjects). Northern Eurasia was represented by Buryats from Ulan-Ude City (50 subjects) and Huromsha Town (50 subjects) (Buryatia), Russians (100 subjects) from Tomsk region, Khants (100 subjects) from Russinskaya village Surgut district (Khant-Mansi Autonomic district), Kets (50 subjects) from Kellog Town (Turukhan district, Krasnoyarsk region), South Kirghizs from Osh Town (50 subjects, and Northern Kirghizs from Kegeti Town (50 subjects) (Kirghizstan Republic). Venous blood withdrawal was conducted after medical examination with written informed concern for study conduction. Ethnicity of each individual was registered up to the third generation.

An analysis of single nucleotide polymorphisms was conducted with the PCR-RFLP protocol. Six SNP markers evenly distributed along *DMPK* gene were selected (Table 1). Examination of the genotype distribution in the examined polymorphic variants for Hardy–Weinberg equilibrium accordance was conducted with the χ^2 test. The haplotype frequencies among populations were determined by the EM algorithm. In probands with MD and their relatives, haplotypes also were established based on segregation analysis of chromosomes carrying mutations and normal chromosomes in their pedigree. To analyze marker association in the examined polymorphic variants with MD disease, the allele and genotype frequencies in patient and healthy subject groups were compared by the χ^2 test and the exact Fisher test. The level of genetic variability and interpopulation differentiation was calculated with the molecular variability (AMOVA) approach. A phylogenetic tree of populations was built with an algorithm of neighbor joining [24] with the use of PHYLIP software [25]. Differences were considered significant at a significance level of $P < 0.05$.

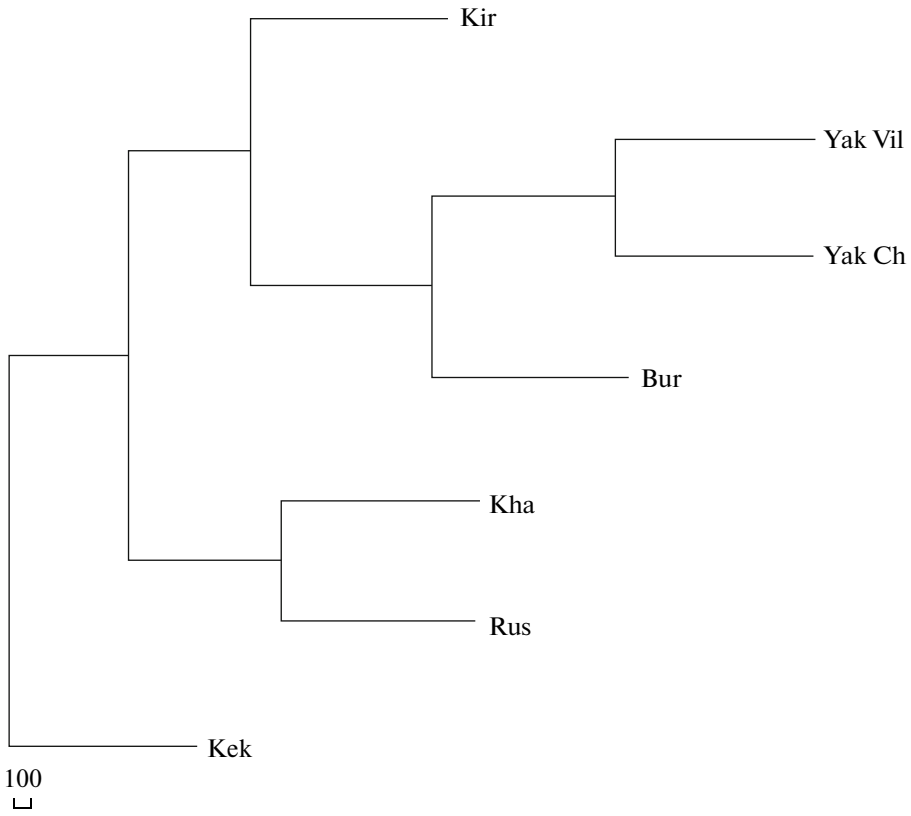
RESULTS AND DISCUSSION

Genetic Variability of Six Single Nucleotide Polymorphic Variants in the DMPK Gene in Northern Eurasian Populations

The allele frequencies, heterozygosity characteristics, and Hardy–Weinberg equilibrium accordance in six polymorphic variants of *DMPK* gene in the examined populations are presented in Table 2. The genotype distribution in all markers in all of the populations was in accordance with Hardy–Weinberg equilibrium. In a comparison of the allele and genotype frequencies between the examined groups at polymorphic locus rs2070736, the lowest value of minor allele frequency (15%) was revealed in Kets, while the highest (37.3%) was found in Yakuts. At polymorphic locus rs572634 the minimum value was observed in Yakuts (9.6%) and the maximum was foun in Kets (36%). At locus rs1799894 the minimum frequency of minor allele was revealed in the population sample of Yakuts (12.1%),

Table 2. Allele frequencies and heterozygosity in the examined population samples

The examined groups	SNP in the *DMPK* gene	Minor allele frequency	The observed heterozygosity (H_o)	The expected heterozygosity (H_e)
Yakuts ($N = 228$)	rs2070736	0.373	0.513	0.470
	rs572634	0.096	0.107	0.127
	rs1799894	0.121	0.195	0.218
	rs527221	0.171	0.272	0.284
	rs915915	0.232	0.382	0.367
	rs10415988	0.132	0.212	0.231
Buryats ($N = 100$)	rs2070736	0.355	0.410	0.458
	rs572634	0.153	0.204	0.259
	rs1799894	0.278	0.414	0.401
	rs527221	0.035	0.070	0.068
	rs915915	0.283	0.343	0.406
	rs10415988	0.245	0.410	0.370
Kirghizs ($N = 100$)	rs2070736	0.337	0.388	0.447
	rs572634	0.180	0.237	0.296
	rs1799894	0.347	0.490	0.453
	rs527221	0.174	0.284	0.287
	rs915915	0.335	0.402	0.446
	rs10415988	0.308	0.434	0.426
Russians ($N = 100$)	rs2070736	0.240	0.420	0.365
	rs572634	0.137	0.232	0.236
	rs1799894	0.449	0.535	0.495
	rs527221	0.143	0.245	0.245
	rs915915	0.336	0.402	0.464
	rs10415988	0.435	0.490	0.492
Khants ($N = 100$)	rs2070736	0.311	0.337	0.429
	rs572634	0.107	0.153	0.191
	rs1799894	0.459	0.469	0.497
	rs527221	0.071	0.121	0.131
	rs915915	0.402	0.392	0.481
	rs10415988	0.474	0.392	0.499
Kets ($N = 50$)	rs2070736	0.150	0.240	0.255
	rs572634	0.360	0.480	0.461
	rs1799894	0.330	0.420	0.442
	rs527221	0.380	0.520	0.471
	rs915915	0.460	0.460	0.497
	rs10415988	0.320	0.440	0.435



Dendrogram of genetic relationships among populations of North Eurasia for studied SNP markers. Kir, Kirghiz; Yak Vil, Yakuts from Viluy District; Yak Ch, Yakuts from Central District; Bur, Buryats; Kha, Khanty; Rus, Russians; Kek, Kets.

and the maximum (45.9%) was found in the Khant population. Deviation of the allelic frequencies at locus rs527221 was as follows: low frequencies were observed in Buryat and Khant populations (3.5 and 7.1%, respectively), while the maximum frequency was noted in the Kets population (38%). For rs10415988 the minimum frequency of the minor allele (13.2%) was noted for Yakuts, while in Khants it reached the maximum in all of the examined groups (47.4%). The analysis of the allele frequency distribution in the majority of the examined loci has demonstrated a closer proximity for the examined population and Asians than for Europeans and Africans [26]. On pairwise comparison of the examined populations for frequencies of the examined loci, significant differences were observed between populations of Kets and Buryats (at all six examined loci), Kets and Khants, and Buryats and Russians (at four loci). The highest level of average exptected heterozygosity in all six examined genetic markers was observed in the Kets population ($H_e = 0.427$), while the lowest was found in the Yakut population ($H_e = 0.283$). A low level of genetic variability within the Yakut ethnicity, which was repeatedly observed in other studies by various marker systems (mtDNA, Y-chromosome, polymorphism of CTG repeats in the *DMPK* gene) in Yakut populations, is typical for isolated ethnic groups [27–32] that originated from a small number of ancestors, which may indicate the founder effect. During analysis of the extent of the observed heterozygosity, the maximum value (0.535) was observed at locus rs1799894 in the Russian population.

During studies of population samples for the *DMPK* gene, we analyzed the genetic relationships for all of the examined populations. The quantitative index of population subdivision (F_{ST}) was determined between two territorial groups of Yakuts (Central and Viluy Districts) and six populations of northern Eurasia (Yakuts, Kets, Russians, Kirghizs, Buryats, and Khants). The importance of genetic differentiation in populations at all of the examined SNP-loci for northern and Asian samples was 11.83%. This index was ten times higher than that for the two Yakut populations (0.79%). This demonstrates population heterogeneity in northern Eurasia as compared with populations residing in Sakha Republic.

In our study, we also analyzed the extent of genetic proximity between two Yakut populations, as well as for all of the examined populations from northern Eurasia, by the genotype frequency of the examined six SNP variants of the *DMPK* gene. To create a dendrogram of genetic distances, we used a database that

Table 3. Allele frequencies and heterozygosity in Yakut samples

The examined groups	SNP in the *DMPK* gene	Minor allele frequency	The observed heterozygosity (H_o)
Yakut MD patients ($N = 98$)	rs2070736	0.276	0.531
	rs572634	0.195	0.102
	rs1799894	0.437	0.730
	rs527221	0.104	0.118
	rs915915	0.212	0.255
	rs10415988	0.448	0.752
Yakuts (population) ($N = 228$)	rs2070736	0.373	0.495
	rs572634	0.096	0.117
	rs1799894	0.121	0.197
	rs527221	0.171	0.265
	rs915915	0.232	0.331
	rs10415988	0.132	0.227

includes populations of Buryats, Kirghizs, Khants, Kets, and Russians, as well as two Yakut populations separated according to residential area: Central or Viluy Districts. The Figure shows a consensus dendrogram, which demonstrates the genetic proximity of Yakut samples and the relative location of the other five examined populations of northern Eurasia.

Analysis of SNP-Allele Distribution Frequencies and the Structure of SNP Haplotypes in the DMPK Gene from Yakut Samples

The allele frequencies and characteristics of heterozygosity in six single nucleotide polymorphic variants of the *DMPK* gene (rs2070736, rs572634, rs1799894, rs527221, rs915915, and rs10415988) were analyzed in groups of MD patients and in the Yakut population (Table 3). The maximum frequency of the minor allele (44.8%) was revealed for polymorphic locus rs10415988 in the group of Yakut patients. The minimum frequency of the minor allele was observed in the population sample of Yakuts in locus rs572634 (9.6%). The maximum value of observed heterozygosity was in Yakut MD patients at loci rs1799894 (0.730) and rs10415988 (0.752). A shortage of heterozygotes in the locus rs572634 (0.102) was also noted in the same group.

A comparison of MD patients with the population sample of Yakuts has shown that the loci rs915915, rs1799894, and rs10415988 were significantly associated with MD. The odds ratios (OR) of MD development in representatives of Yakut population at these loci were estimated as 2.59 (95% CI, $p = 0.004$), 4.99 (95% CI, $p = 0.000$), and 3.15 (95% CI, $p = 0.01$), respectively.

We also analyzed the revealed haplotypes at the polymorphic mononucleotide sites of the *DMPK* gene in the examined samples of subjects of Yakut ethnicity. With the EM algorithm, 25 haplotypes with frequencies from 0.003 to 0.39 were revealed in the group of MD patients. At the same time, only two haplotypes, TTTCTC and GTCCTT, were revealed, and they comprised 58% of the entire database. Haplotype TTTCTC was observed with the maximum frequency (38.9%). We obtained similar results during studies of the family data for Yakut patients with MD via a pedigree analysis. A comparison of the results of haplotype analyses conducted with two different approaches is presented in Table 4. Segregation analysis of chromosomes carrying mutations and normal chromosomes in pedigrees revealed 19 haplotypes in 24 families of MD patients. The frequencies of major haplotypes were independent of the analytype and did not change

Table 4. Frequencies of SNP haplotypes in the population of MD Yakut patients revealed by two different approaches

MD patient haplotype	Haplotype frequency calculated using EM algorithm, % ($N = 98$)	Haplotype frequency calculated by the analysis of family data, % ($N = 60$)
TTTCTC	38.9	40.0
GTCCTT	19.3	18.3
TTCCGT	5.5	4.2
TTTCTT	2.2	6.7
TTCCTC	3.1	5.0
GTTCGT	2.7	3.3
GTCCGT	3.1	3.3

Table 5. Frequencies of major SNP haplotypes and the results of pairwise comparison of MD patients with the Yakut population sample

Haplotype	Haplotype frequency, %		χ^2	P	OR
	MD patents ($N = 60$)	population ($N = 228$)			
TTTCTC*	40.0	7.5	88.09	0.000	8.22
GTCCTT*	18.3	5.5	20.78	0.000	3.83
TTCCGT*	4.2	31.5	36.22	0.000	0.09
TTTCTT*	6.7	0.3	22.97	0.000	19.93
TGCCGT*	3.3	0.5	5.09	0.024	6.4
GTCCGT*	3.3	27.5	31.02	0.000	0.09

* Frequencies are significantly different ($P \le 0.05$).

Table 6. Haplotype frequency in six SNP loci of the *DMPK* gene in MD patients

Haplotype	Canada [33]	Japan [34]	Taiwan [14]	Korea [22]	Yakuts (this study, 2013)
TTTCTC	49	30	41	41.4	40.0
GTCCTT	–	–	–	–	18.3
TTCCGT	8	53	21	19.7	4.2
GTCCGT	27	–	11	20.4	3.3
TTCGGT	–	4.8	4	6.6	–

significantly. Both approaches revealed two major haplotypes, TTTCTC and GTCCTT, which were typical in MD Yakut patients. The frequencies of major haplotype manifestations among Yakut MD patients were 40.0 and 18.3%, respectively. At the same time, the "major" haplotype TTTCTC was revealed on the chromosome with expansion of three nucleotide repeats in 54.2% cases of MD patients and in 63.3% cases in probands. This again undeniably supports the notion of the importance of this haplotype in the development in the examined disease.

In the Yakut population sample, we found 26 haplotypes, the frequencies of which varied from 0.02 to 0.315. Eighteen haplotypes were observed with a frequency of less than 1%, and only two haplotypes comprised approximately equal ratios according to incidence: the GTCCGT haplotype was observed with a frequency of 27.5% and the TTCCGT haplotype was observed with a frequency of 31.5%.

Table 5 shows the characteristics of common haplotypes found in MD patients and in the Yakut population sample as well as the results of pairwise comparison of these haplotype frequencies. In a comparison of the MD patient group and the Yakut population sample, we observed six major common haplotypes. In all of the common haplotypes, significant differences in the frequencies of incidence were observed. These are the haplotypes TTTCTC (OR = 8.22, 95% CI 4.94–13.70), GTCCTT (OR = 3.83, 95% CI 2.04–7.16), TTCCGT (OR = 0.09, 95% CI 0.03–0.25), TTTCTT (OR = 19.93, 95% CI 3.86–137.71), TGCCGT (OR = 6.4, 95% CI 1.19–36.51), and GTCCGT (OR = 0.09, 95% CI 0.03–0.26). High indices of the risk for disease development (OR) were found in the case of four haplotypes: "major" haplotype TTTCTC, as well as for GTCCTT, TTTCTT, and TGCCGT. At the same time, haplotype GTCCTT in MD patients was found with equal frequency (18.3%) both in chromosomes

carrying the mutation and in normal ones. We concluded that haplotype TTTCTC is risky; it is located on a mutant chromosome in 63.3% cases (versus in 16.6% cases, where it is located on a chromosome without mutation). This demonstrates a high odds ratio value (OR = 8.22). In contrast, the index of the odds ratio appeared to be below zero for haplotypes TTCCGT and GTCCGT, which could have protective importance in light of the fact that these haplotypes in all of the examined families were located only on chromosome carrying the mutation.

A comparison of the obtained haplotype data with those previously obtained in other studies [14, 22, 33, 34] demonstrates that major haplotype TTTCTC was observed in MD patients in different countries with approximately equal frequencies to those in our study (Table 6). Another two haplotypes (TTCCGT and GTCCGT) were observed in MD patients of various ethnicities with various frequencies. Haplotype GTCCTT, which was observed in our study with a high frequency (18.3%), was typical only for Yakut MD patients.

Therefore, in our study we presented population and genetic characteristics of six populations of northern Eurasia (Yakuts, Buryats, Kets, Khants, Russians, and Kirghizs) in six single nucleotide polymorphic variants in the *DMPK* gene. In the Yakut sample we revealed three polymorphic variants (rs915915, rs1799894, and rs10415988) associated with myotonic dystrophy. We also have shown the haplotype structure of six SNPs in MD patients of the Yakut sample. Haplotype TTTCTC, which is associated with the disease, was revealed with a high frequency (40.0%), and haplotypes TTCCGT and GTCCGT, which might have protective importance with respect to MD, were identified. In addition to SNP haplotypes, which are common for many world populations, we revealed haplotype GTCCTT, which is unique for Yakut MD patients and was observed with high frequency.

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