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HUMAN GENETICS

Haplotype Analysis of Oculopharyngeal Muscular Dystrophy (OPMD) Locus in Yakutia

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Abstract—Oculopharyngeal muscular dystrophy (OPMD) is a hereditary neuromuscular disease with autosomal dominant and rarely with autosomal recessive inheritance types. This study included 50 patients with a clinical diagnosis of OPMD, 23 asymptomatic carriers of the mutation from 45 unrelated families, and 56 healthy relatives, as well as population samples of four ethnic groups of Yakutia: Yakuts, Evens, Evenks, Yukaghirs. It was found that the cause of OPMD development in all investigated families is the same increase in GCN repeats to 14 copies in the *PABPN1* gene. The molecular structure of the $(GCN)_{14}$ mutant allele is $(GCG)_{10}(GCA)_3GCG$. The genetic variability of ten SNPs at the OPMD locus was studied in patient families and population samples. The haplotypes of OPMD were determined by a segregation analysis technique and using the EM algorithm in the groups of patients, mutation carriers, and population samples. Only one haplotype of four SNPs (ATCG) linked with the $(GCN)_{14}$ mutant allele was found in Yakuts and Russian patients and OPMD mutation carriers. Probably, this indicates the accumulation of mutations as a result of the founder effect.

Keywords: oculopharyngeal muscular dystrophy, *PABPN1*, haplotype analysis, Yakuts
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INTRODUCTION

Oculopharyngeal muscular dystrophy (OPMD, OMIM 164300) is a hereditary neuromuscular disease with autosomal dominant type of inheritance, which is manifested in the fifth to sixth decade of life. Also, the cases of recessive inheritance type have been described [1, 2].

In 1998, Brais et al. mapped the gene of poly(A) binding protein 2 (*PABPN1*), responsible for the synthesis of nuclear protein PABPN1 (mRNA polyadenylation factor), on chromosome 14q11.2-13 and identified the mutation consisting in increase in the number of copies of trinucleotide GCN repeats in the first gene exon. Normally, the gene contains 10 tandem copies of GCN repeats, while the number of repeats varies from 11 to 17 copies in patients [3, 4]. The region of GCN repeats encodes 10 alanines. Normal allele $(GCN)_{10}$ of the gene has the following structure—$(GCG)_6(GCA)_3(GCG)$. Expansion of this region may occur owing to a simple increase in GCG triplets [5, 6] or by GCA insertions along with the increase in GCG triplets [7, 8]. There are cases where the expansion of GCN repeats occurs owing to a point mutation ($G \rightarrow C$) in a GGG triplet, which encodes glycine and is located immediately after the region of GCN repeats. This GGG repeat is followed by two GCG triplets, leading to an increase in GCN repeats to 13 and formation of the pathology [9].

Initially, it was believed that the disease is caused by the expansion of only GCG repeats, but as it turned out later, the structure encoding ten alanines also has GCA insertions. Since GCA and GCG encode the same amino acid, it was decided to designate the triplet whose expansion leads to OPMD as GCN [8, 10].

The mechanism of tandem repeat expansion in OPMD is still unclear. It has been suggested that it may be associated with unequal crossing over, a type of homologous recombination which occurs in germ cells during meiosis or mitosis [11]. The increase in the number of repeats per GCN repeat under heterozygous carriership does not lead to OPMD and is considered as a polymorphism, but patients homozygous for $(GCN)_{11}$ (autosomal recessive OPMD) with a mild form of the disease with late onset of clinical symptoms have been described [12, 13].

On the basis of the analysis of the results of genetic and epidemiological studies on Mendelian pathology in the population of the Republic of Sakha (Yakutia),

several forms of the pathology called "Yakut" hereditary diseases with a high prevalence among Yakuts compared with the global population were previously identified: spinocerebellar ataxia type 1, myotonic dystrophy, enzymopenic hereditary methemoglobinemia, and 3-M syndrome [14]. OPMD also belongs to these diseases [15].

We found that the cause of OPMD in all investigated families is the same increase in GCN repeats to 14 copies in the *PABPN1* gene. The $(GCN)_{14}$ mutation was detected in all 50 patients. Asymptomatic carriership of the $(GCN)_{14}$ mutation was revealed in 23 clinically healthy relatives. The structure of identified mutation is $(GCN)_{14}$–$(GCG)_{10}(GCA)_3(GCG)$; the region encodes 14 alanines [15, 16].

The studies on OPMD haplotype analysis using short tandem repeats (STRs) or single nucleotide polymorphisms (SNPs) as markers are rare in the world [1, 9, 17]. In Russia, such studies have not been carried out yet.

The aim of this study is to describe the genetic variability, identify the structure and the prevalence of SNP haplotypes at the locus of the *PABPN1* gene in the populations of Yakutia and patients with OPMD, and evaluate the possible population and genetic causes of the OPMD distribution among Yakuts.

MATERIALS AND METHODS

The study included 50 patients with a clinical diagnosis of OPMD from 45 unrelated families (45 patients from 42 Yakut families, five patients from three Russian families) and 56 healthy relatives. Twenty-three carriers of the mutation of Yakut nationality without clinical symptoms of the disease were also investigated from these families. The population sample was composed of four ethnic groups living in the territory of Yakutia: Yakuts ($n = 300$), Evens ($n = 70$), Evenks ($n = 50$), Yukaghirs ($n = 25$). For comparison, the data on four population samples of the International HapMap project were used: Chinese ($n = 36$), Japanese ($n = 38$), natives of Northern and Western Europe (United States) ($n = 46$), Yoruba (Nigeria) ($n = 52$). Sequencing on an ABI PRISM 3100 automated DNA analyzer (Applied Biosystems) was performed to determine the structure of the identified mutation.

Eleven variants of single nucleotide polymorphism (SNP) were chosen as markers to study the OPMD locus. The spacing between the outermost markers is 20581 base pairs at the locus of the *PABPN1* gene, flanking the region of GCN repeats.

Genotyping was performed by PCR-RFLP. Table 1 shows eleven studied SNPs, their position on the chromosome, the structure of primers, annealing temperature, and restriction enzymes. Primers described in the literature were used for two SNPs (rs2239579 and rs1054084) [18, 19].

Genotyping conditions for the other nine SNPs were selected in this study. SNP rs1054084 was excluded from further analysis because of its monomorphism. Genotyping conditions for rs1950252 and rs2295126 were developed by PCR-RFLP using native restriction sites (Table 1).

Modified primers leading to the emergence of an artificial restriction site for the corresponding enzyme were designed for six SNPs (rs2231301, rs1535094, rs7142474, rs2268330, rs7161120, rs481469) (Table 1).

The mutation at the locus of trinucleotide GCN repeats is located between the fifth and sixth SNPs (rs2239579 and rs8020117). The standardized measure of linkage disequilibrium D' was calculated according to Lewontin [20]. A strong linkage between the loci corresponds to $D' = 1$ and LOD ≥ 2 (LOD score, the logarithm of odds for and against the linkage). The blocks of linkage disequilibrium determined by Haploview 4.0 software using the solid spine algorithm.

The EM algorithm (expectation maximization) implemented in Haploview 4.0 and Arlequin software was used to calculate haplotypic frequencies [21].

Along with the use of the EM algorithm, the haplotype structure according to ten studied polymorphic variants was determined using family-based analysis proceeding from the homozygous state of the SNP in each locus, where it was possible (by direct observation).

Phylogenetic analysis of the SNP haplotype relationships was performed by constructing phylogenetic trees of the haplotypes according to the median joining (MJ) network algorithm implemented in Network software [22]. Statistical processing of the results was performed using the following statistical software: Microsoft Office Excel 2007, Arlequin 3.5.1.3, Haploview 4.0, Network 4.5.1.6.

RESULTS AND DISCUSSION

SNP Haplotype Structure and Linkage Disequilibrium at the OPMD Locus

Fifteen multilocus genotypes of ten SNPs were found in the sample composed of the carriers of the $(GCN)_{14}$ mutation (patients and healthy persons) with the total number of 73 persons, where 68 of them were Yakuts, and five were Russians. According to the results of the genotyping, it was found that all the studied individuals were heterozygous carriers of the $(GCN)_{14}$ mutation.

The analysis of SNP haplotype structure and linkage disequilibrium (LD) at the OPMD locus using EM algorithm revealed 52 haplotypes in the studied groups of Yakut and Russian patients, their healthy relatives, and population samples. The greatest number of haplotypes was observed in Yakuts (35), the smallest was in Russian patients (2). The haplotype frequency was from 0.2 to 71.8%. In total, the study identified 14 major

Table 1. Primer sequences and PCR conditions

Gene	Polymorphism	Structure of primers	Tm, °C; restriction enzyme	Localization	Reference
PABPN1	$(GCN)_{14}$ exon 1	F: 5'-cgcagtgccccgccttaga-3' R: 5'-acaagatggcgccgccgccccggc-3'	60	860513–860561	[25]
BCL2L2	rs2231301 exon 3	F: 5'-tcatgccagtctttcatcctt-3' R: 5'-aactcatctccagctgcccgcatggcttggt*a*cag-3'	65 *Bst*4CI	846939	–
	rs1950252 exon 4	F: 5'-tgtgcatgctgggctgcctggcaaatctggtggtg-3' R: 5'-cagaactgctcttctctccaaag-3'	60 *Asu*HPI	848538	–
	rs1535094 exon 4	F: 5'-tttggaactcgcagtcctct-3' R: 5'-aatctccaagaagagtcaaccatggtctagct*c*ag-3'	65 *Pvu*II	849474	–
	rs7142474 intergenic	F: 5'-cgtcttctggggcacagtat-3' R: 5'-aaaaaataaatgaatgaatactcgtatttag*g*atc-3'	63 *Bam*HI	855445	–
PABPN1	rs2239579 exon 1	F: 5'-cctggatggggaaagtaagc-3' R: 5'-gaggcccaaaacagagcagc-3'	64 *Hsp*AI	859899	[18, 19]
	rs8020117 intron 2	F: 5'-acgctttaggattctaagagaaagc-3' R: 5'-cagtacgtacattgccaacatagat-3'	60 *Taq*I	861859	–
	rs2295126 exon 3	F: 5'-ctgctatgcactaggcactattctc-3' R: 5'-aataattccccaaaagaagaacttg-3'	56 *Asu*HPI	862055	–
	rs1054084 exon 7	F: 5'-aaaacagaagatgaccttgatgga-3' R: 5'-gggaaggtaacaagcagaacagtt-3'	54 *Hsp*AI	864647	[18]
	rs2268330 3'-UTR	F: 5'-gaaaaggtagctgggtgcag-3' R: 5'-tactgacctaatggcgcttttgtgtgctcctg*g*ta-3'	60 *Rsa*I	865816	–
	rs7161120 3'-UTR	F: 5'-ggaggtggagattgaggtga-3' R: 5'-taacccataacagaaagtagaataaatgacc*gg*at-3'	52 *Bam*HI	867041	–
	rs4981469 3'-UTR	F: 5'-aaaattcctaaaaaaagtactttaaaagatag*t*gt-3' R: 5'-agaagtttggaggctgagca-3'	64 *Bst*MAI	867520	–

Replaced nucleotides are underlined in the primer sequences; Tm, temperature of primer annealing; localization at chromosome is indicated according to the reference sequence of the NCBI database (URL = http://www.ncbi.nlm.nih.gov).

haplotypes occurring with a frequency of more than 5% (Table 2).

The most frequent haplotype revealed by direct analysis coincides with the most frequent haplotype according to the EM algorithm (haplotype 1, see Table 2). The sequence of this haplotype (GGGATCGCCC) was detected in 20% of the mutation carriers and Yakut patients. The other two haplotypes, detected in homozygotes of ten SNPs, GGGATCGGCC (17.65%) and GGGATCGGCG (1.47%), were in line with haplotypes 3 and 9, identified according to the EM algorithm.

Thus, three haplotypes are restored in the carriers of the mutation of ten SNPs, which are unambiguously associated with the mutation. The most probable ancestral haplotype carrying the mutation is haplotype 1 (GGGATCGCCC). It is detected with a higher frequency in patients and the carriers of Yakut mutation by direct observation of homozygotes of ten SNPs, as well as using the EM algorithm.

Figure 1 shows the structure of LD between the studied markers of the OPMD locus in population samples of Yakutia and four populations of the international HapMap project. Three blocks of linkage were found in Yakuts: block 1 consists of three closely located polymorphic variants (rs2231301, rs1950252, and rs1535094); block 2 includes four adjacent SNPs (rs7142474, rs2239579, rs8020117, and rs2295126); block 3 consists of two polymorphic variants (rs7161120 and rs4981469). One block comprising a different number of SNPs was found in each remaining population. The Evenk population, where two blocks were found, was an exception. Probably, three blocks of linkage, found only in Yakuts, are the result of a larger sample rather than a lack of recombination at this region in other ethnic groups. It should be noted that two haplotypes exhibiting the association with the disease are the most frequent and are found in Yakut mutation carriers, as well as in Russian patients, while the third is relatively rare and was found only in Yakuts. Haplotypes 1 and 3 can be obtained from one another by recombination between two SNP blocks, identified in HaploView 4.1. Haplotype 9 is either the result of a mutation that occurred in haplotype 3 or the result of recombination within the third SNP block.

Table 2. Distribution of haplotype frequencies (in %) of ten SNPs at the OPMD locus in studied samples

No.	Haplotype 1 2 3 4 5 6 7 8 9 10	Yakut patients and carriers of the mutation ($N = 68$)	Russian patients and carriers of the mutation ($N = 5$)	Healthy relatives ($N = 56$)	Yakuts ($N = 298$)	Evenks ($N = 50$)	Evens ($N = 70$)	Yukaghirs ($N = 25$)	Europeans ($N = 46$)	Japanese ($N = 36$)	Chinese ($N = 38$)	Yoruba ($N = 52$)
1	**GGGATCGCCC**	**48.6**	**40.0**	**32.7**	**7.9**	**1.6**	**13.3**	**48.0**	**68.4**	**48.7**	**36.1**	**71.8**
2	GGGATCGCCG	2.9	–	1.8	5.6	3.0	16.9	10.0	–	–	–	–
3	***GGGATCGGCC***	***14.4***	***60.0***	***5.7***	***35.9***	***41.4***	***15.1***	–	–	–	–	–
4	AGGACCGGCG	14.6	–	27.7	0.5	2.0	18.4	10.0	23.9	35.5	52.8	–
5	AGGATCGGCG	1.5	–	4.8	0.9	13.5	–	2.0	1.1	–	–	–
6	AGGACCGCCC	–	–	–	10.3	3.0	–	–	–	–	–	–
7	AGGACCGCCG	–	–	3.9	16.8	9.9	12.7	2.0	1.1	–	–	–
8	GGGACCGCCG	–	–	2.2	1.6	14.0	2.6	–	–	–	–	–
9	***GGGATCGGCG***	***7.1***	–	***9.1***	***6.6***	***1.0***	***3.8***	***2.0***	***2.2***	–	–	–
10	GGGACCGGCG	6.1	–	6.7	3.8	–	1.8	14.0	–	2.7	2.8	–
11	AGGATCGCCC	–	–	–	3.0	–	–	–	–	–	–	1.9
12	AGGATCGCCG	–	–	–	0.9	8.5	4.5	8.0	–	–	–	–
13	GGGATCACCC	–	–	1.0	0.2	–	–	–	3.3	3.9	1.4	17.6
14	AGGACCGGCC	–	–	1.1	0.8	–	8.0	–	–	–	–	–
15	Other haplotypes	4.8	0	3.3	5.2	2.1	2.9	4	0	9.2	6.9	8.7
	Number of found haplotypes	13	2	14	35	12	13	10	6	10	6	10

N (in Tables 2, 3) is the number of individuals in the sample. Ancestral haplotype of OPMD patients and carriers of the mutation is in bold; haplotype frequencies found in OPMD patients and carriers of the mutation of homozygous ten-locus genotypes are in bold italics. The order of SNPs in haplotype: (1) rs2231301, (2) rs1950252, (3) rs1535094, (4) rs7142474, (5) rs2239579, (6) rs8020117, (7) rs2295126, (8) rs2268330, (9) rs7161120, (10) rs4981469.

Phylogenetic Analysis of Haplotypes at the OPMD Locus

Phylogenetic analysis of haplotypes of the second block of linkage (which includes the OPMD mutation) found in the Yakut population was carried out in this work.

The median joining network of the haplotypes of the LD second block linked with the $(GCN)_{14}$ mutation, of two groups of OPMD patients (Yakuts and Russians), of one sample of their healthy relatives, and of eight ethnic samples is shown in Fig. 2. Table 3 represents the haplotype frequencies. The ancestral haplotype defined according to the National Center for Biotechnology Information (NCBI, United States) and shown by the arrow was found in almost all samples except Russian, Evenk, and Yukaghir patients and has ATCA allelic structure (SNP 4–7; Ht4). This haplotype initial for humanity is the most frequent in the Yoruba sample (17.6%, see Table 3). A relatively high haplotype diversity compared with other samples was found in the African population of Yoruba (6 out of 11 possible). The Yakut population sample is characterized by five haplotypes. Four haplotypes (ATCG, ACCG, ATCA, GTTG) were found in Yakut patients and OPMD carriers, and five in healthy relatives.

One haplotype associated directly with the $(GCN)_{14}$ mutation was identified by direct analysis in the patients of the Russian group, as well as the Yakut group, which is most likely a founder haplotype (Ht5; ATCG, see Fig. 2). The same haplotype is present in all five Russian OPMD patients. It is spaced from the ancestral haplotype according to the NCBI base (ATCA) by one mutational step (ATCG).

According to the study results, the greatest number of haplotypes is found in the Yoruba population,

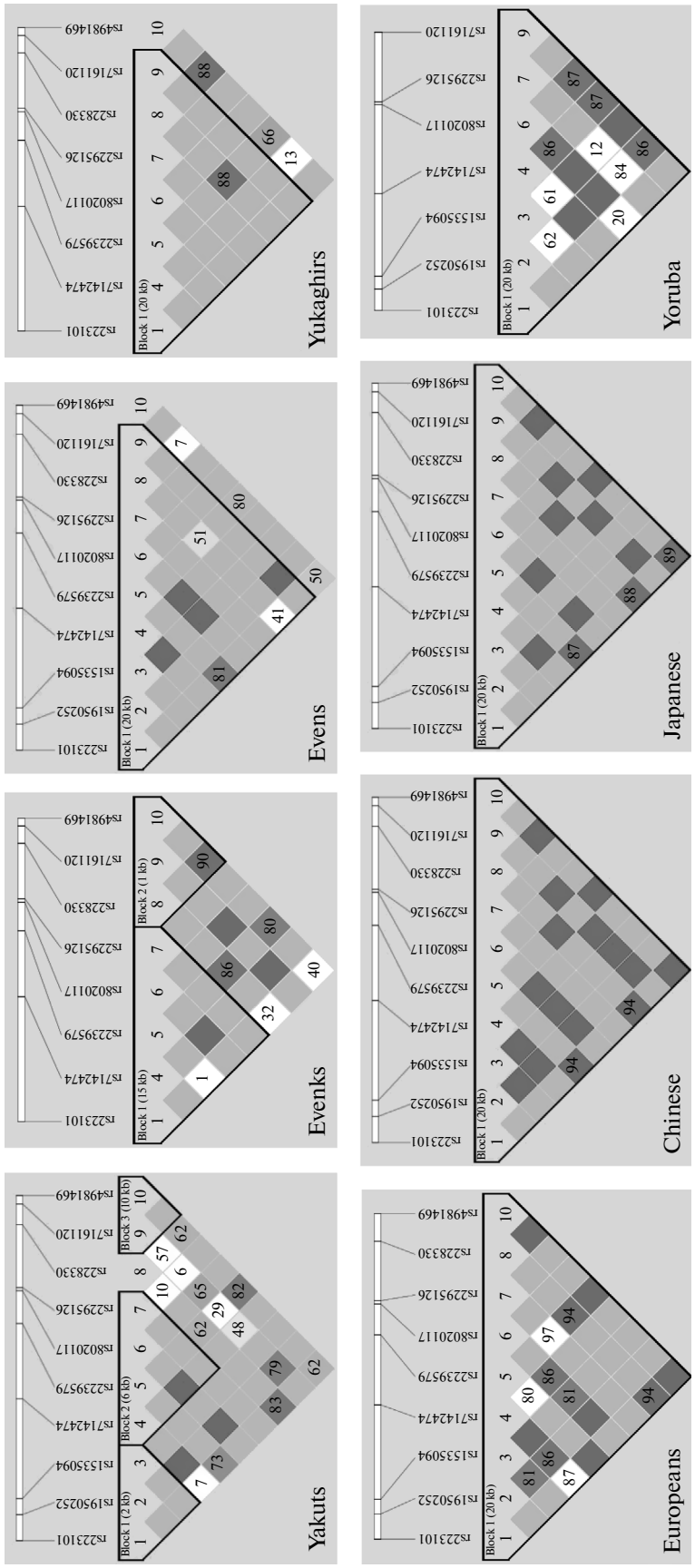

Fig. 1. Structure of linkage disequilibrium at the OPMD locus in studied populations. The color scale indicates the strength of linkage between SNPs: (dark gray) strong linkage ($D' = 1$, LOD ≥ 2); (gray) significant linkage ($D' < 1$, LOD > 2); (white) poor linkage ($D' < 1$, LOD < 2). The cell in light gray means the impossibility to calculate the linkage disequilibrium owing to the low frequency of the minor allele polymorphism ($D' = 1$, LOD < 2). The variants of the polymorphism rs2231301, rs1950252, rs1535094, rs7142474, rs2239579, rs8020117, rs2295126, rs1054084, rs2268330, and rs7161120 are numbered from 1 to 10, respectively.

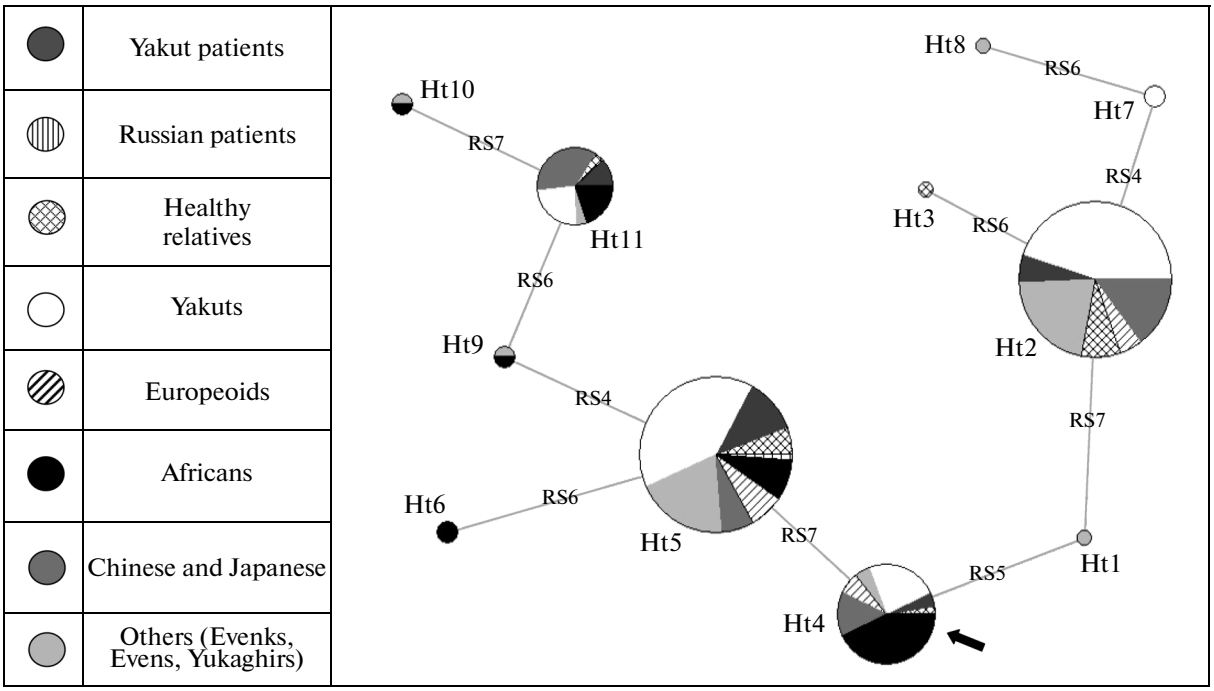

Fig. 2. Median joining network of haplotypes (Ht) for the groups of OPMD patients and carriers of the mutation, samples of healthy relatives of Yakut OPMD patients, and eight ethnic samples based on four SNPs: rs7142474, rs2239579, rs8020117, rs2295126 (the second LD block of Yakuts).

healthy relatives of Yakut OPMD patients, and the Yakut population (six, five, and five haplotypes, respectively). The populations of Evenks, Evens, Yukaghirs, Chinese, and Japanese and a sample of Yakuts, OPMD mutation carriers, were characterized by the presence of four haplotypes. Three haplotypes were found in Europeans.

DISCUSSION

It was found that the cause of OPMD development in all families examined in this work is the same increase in GCN repeats to 14 copies in the *PABPN1* gene. The structure of the identified mutation was determined: $(GCN)_{14}$–$(GCG)_{10}(GCA)_3(GCG)$. A similar expansion of GCN repeats in the first exon of the *PABPN1* gene by a simple increase in the number of GCG repeats was previously found in other populations of the world: in Cajuns (French-speaking residents of Louisiana, United States) [2], Germany [11], Italy [7], Thailand [23], and Great Britain [24]. But all the described cases are single instances [1, 10, 18, 25, 26]. Accumulation of OPMD in the world in individual populations is mainly caused by $(GCN)_{11}$, $(GCN)_{12}$ [27], $(GCN)_{13}$ [1, 19, 28], and $(GCN)_{15}$ mutations [18, 19].

The comparative study showed that the structure of linkage disequilibrium in the *PABPN1* gene is population specific and varies in all six studied populations. The maximum number of haplotypic blocks (3) was noted in Yakuts, while the minimum number (1 block) was noted in Evens, in Yukaghirs, and in the populations of the international HapMap project (www.hapmap.org)—Japanese, Chinese, Europeans, and Africans (Yoruba). A varying degree of haplotype diversity observed in the studied populations was characterized by the presence of the same main haplotypes for all the samples.

Three haplotypes carrying the mutation were identified in ten locus SNP haplotypes. Taking into account the block structure of linkage disequilibrium within the block of disequilibrium, which includes the point of the mutation, one haplotype (ATCG) linked with the mutant $(GCN)_{14}$ allele was found, which is probably indicates the accumulation of the mutation as a result of the founder effect.

To date, it is known that the high frequency of OPMD is found only in three or four populations in the world, which are characterized by a strong founder effect. Considering that a high frequency of OPMD is also noted for the Yakut population according to the results of this study, the founder effect in the early stages of ethnogenesis can be assumed. Perhaps, it is caused by passing through the "bottleneck" of the Yakut population in the process of ethnogenesis. In this case, very low haplotype diversity should be observed at the time of a significant reduction in the number of Yakuts, followed by the growth of molecular diversity of haplotypes. The low level of genetic diversity in Yakut populations compared with other populations of Eurasia has been shown under analysis of the lines of

Table 3. Distribution of haplotype frequencies (in %) of the OPMD locus in studied samples of the second block of linkage of the Yakut population sample

Haplotype number (Ht)	Haplotype 4 5 6 7	Yakut patients and carriers of the mutation ($N = 68$)	Russian patients and carriers of the mutation ($N = 5$)	Healthy relatives ($N = 56$)	Yakuts ($N = 298$)	Evenks ($N = 50$)	Evens ($N = 70$)	Yukaghirs ($N = 25$)	Europeans ($N = 46$)	Japanese ($N = 36$)	Chinese ($N = 38$)	Yoruba ($N = 52$)
Ht1	ACCA	–	–	–	–	1.00	–	–	–	–	–	–
Ht2	ACCG	20.77	–	42.71	36.58	29.00	43.57	26.00	25.00	42.11	55.56	–
Ht3	ACTG	–	–	1.04	–	–	–	–	–	–	–	–
Ht4	**ATCA**	1.54	–	1.04	1.68	–	1.43	–	3.26	6.58	1.39	17.54
Ht5	***ATCG***	***75.38***	***100.00***	***54.17***	***60.39***	***69.00***	***54.29***	***70.00***	***71.74***	***46.05***	***36.11***	***73.79***
Ht6	ATTG	–	–	–	–	–	–	–	–	–	–	1.94
Ht7	GCCG	–	–	–	0.34	–	–	–	–	–	–	–
Ht8	GCTG	–	–	–	–	1.00	–	–	–	–	–	–
Ht9	GTCG	–	–	–	–	–	–	2.00	–	–	–	0.98
Ht10	GTTA	–	–	–	–	–	–	2.00	–	–	–	0.73
Ht11	GTTG	2.31	–	1.04	1.01	–	0.71	–	–	5.26	6.94	5.02
Number of haplotypes		4	1	5	5	4	4	4	3	4	4	6

Ancestral haplotype is in bold; possible founder haplotype of OPMD spread in the Yakut population is in bold italics.

mitochondrial DNA, Y chromosome, autosomal microsatellite loci (STR), and Alu repeat loci [29].

Several forms of ethno-specific pathology called "Yakut" hereditary diseases were distinguished on the basis of the data of genetic and epidemiological studies of the Yakut population. Along with OPMD, the "Yakut" hereditary diseases include spinocerebellar ataxia type I (OMIM 164400), myotonic dystrophy (OMIM 160900), enzymopenic hereditary methemoglobinemia type I (OMIM 250800), "Yakut short stature syndrome" (or 3-M syndrome (OMIM 273750)), autosomal recessive deafness type 1A (OMIM 220290), short stature syndrome with optic nerve atrophy, and Pelger-Huet anomaly (or SOPH syndrome (OMIM 614800)) [30]. The prevalence of these diseases is much higher than in the world population. The molecular features which distinguish them from similar phenotypes in other populations in which they occur less frequently have been identified for each disease [14]. Previously, genetic variability and the structure of SNP haplotypes of the *DMPK* gene were studied in Yakuts and other ethnic groups of Northern Eurasia in connection with myotonic dystrophy [31].

The results of this study indicate that OPMD, as well as other ethno-specific diseases of Yakuts, has spread with high frequency owing to the founder effect. Since the haplotype of the OPMD locus, which is ancestral for Yakuts, was found in the Russian population of Irkutsk oblast, it can be assumed that this haplotype is quite ancient and was spread, probably, with a low frequency in the vast territory of Eurasia. Perhaps, it has become widespread in Yakutia as a result of the founder effect during the migration of the Yakut ancestors over the territory of the modern Republic of Sakha (Yakutia).

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