# Clinical-genetic characteristic of Charcot-Marie-Tooth disease 1A type in the Republic Sakha (Yakutia)

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**Summary.** Charcot-Marie-Tooth disease (CMT) - a heterogeneous group of hereditary diseases of the nervous system, characterized by symptoms of progressive polyneuropathy, mainly affecting the muscles of the distal extremities. Frequency in the world is 1 in 2,500. The most common is form of CMT 1A with autosomal dominant inheritance (OMIM118220). In the Republic of Sakha (Yakutia) of CMT type 1A is one of the most common of the hereditary neuromuscular diseases.

**Purpose:** To provide clinical and genetic characteristics of the Charcot-Marie-Tooth disease type 1A in the Republic of Sakha (Yakutia).

**Materials and Methods:** Cases of own and retrospective clinical supervision of patients registered in data of «Republican genetic register of hereditary and congenital pathology in RS (Y)» of the Medical-genetic consultation of Republican hospital №1 - the National Centre of Medicine, annual reports of neurologists from all the republic, materials of the Neurologic department Republican hospital №2 –Medical Emergency Centre, mobile medical inspections over the republic have been analyzed.

**Results and discussion:** The general prevalence of Charcot-Marie-Tooth in Republic Sakha (Yakutia) for January, 1st, 2013 has counted 11,8 per 100 thousand population. The diagnosis of Charcot-Marie-Tooth disease 1A type has been detected on the basis of the molecular-genetic analysis of 43 patients from 113, which is 38 % of all CMT forms. The prevalence of CMT 1A type in the republic has amounted 4,5 per 100 000 population. As regards sexual sign the patients were distributed as follows: men - 25, women – 18; ethnicity: Russian - 15 (35 %), Yakuts - 28 (65 %).

Middle age of patients has been 32,2±15,7 years. The manifestation middle age has amounted 13,0±9,7 years. The average disease duration has amounted 18,6±13,3 years. As first symptoms patients have noted feet deformation, toe defect, gait worsening, weakness and pain in feet, frequent falling. In the clinical picture hypo- or areflexia of lower extremities (84 %) and feet deformation of Fridreich's or hollow type (Tabl.2) have been revealed practically at all patients undergone the survey (in 40 cases (93 %)). Also the patients had muscular atrophy of lower and upper extremities (70 and 49%), sensory defect of polyneuritic type (70%), distal muscular weakness of extremities (93 %). The gait worsening in 35 cases was of steppage type (93 %). Scoliosis has been revealed in 19 % of cases.

Fragment analysis method using markers *D17S2218, D17S2223, D17S2229* was investigated sample of healthy individuals of Yakut ethnic group (n = 100) to establish heterozygosity for these markers. By markers *D17S2218* and *D17S2229* revealed a high heterozygosity (to 76%), i.e. these markers are informative in the Yakut ethnic group. Marker *D17S2223* was less informative because heterozygosity was 49%.

**Conclusions:** The general prevalence of Charcot-Marie-Tooth in Republic Sakha (Yakutia) for January, 1st, 2013 has counted 11. 8 per 100 thousand population. The prevalence of CMT 1A type in the republic has amounted 4. 5 per 100 000 population. The clinical picture of the disease was detected varying severity of polyneuropathy syndrome and feet deformity, with a middle age of manifestation 13,0 ± 9,7 years. For the diagnosis of type CMT 1A in the Yakut population recommended markers *D17S2218* and *D17S2229*.

**Keywords:** Charcot-Marie-Tooth disease type 1A, the gene *PMP22*, prevalence, DNA fragment analysis.

## INTRODUCTION

Charcot-Marie-Tooth (CMT, hereditary motoric-sensorneuropathy, HMSN) is a widely spread group of hereditary diseases of the nervous system characterized by chronically progressing weakness and distal muscular atrophy of extremities, decrease of tendon reflexes, foot and handed formation, gait worsening and sensory defect [5]. The prevalence of CMT in the world amounts 1 per 2500 persons [8]. In Russia this indicator makes 5,64 per 100 thousand population on the average with fluctuations from 1,07 to 15,95 [4]. Now about 50 loci and 30 various genes responsible for formation of CMT phenotype are identified [13].CMT 1A with autosome -dominant type of inheritance (OMIM 118220) is considered the most widespread form [2]. The reason is the mutation in gene *PMP22* (peripheral myelinprotein). Duplication of 1,5 Mb in the field of a chromosome 17p11.2-12 refers to the basic type of this gene mutation [2,8,9,12]. The leading place in structure of genetic pathology in the Republic of Sakha (Yakutia) is occupied by hereditary diseases of the nervous system [3]. Thus among all monogenic neurologic diseases nervous -muscular illnesses are the leading ones, CMT being one of the most widespread in this group [3,6,7].

In this work results of clinical-genealogical and molecular-genetic research of CMT 1A type in RS (Y) are presented.

## MATERIAL AND RESEARCH METHODS

Cases of own and retrospective clinical supervision of patients registered in data of «Republican genetic register of hereditary and congenital pathology in RS (Y) » of the Medical-genetic consultation of Republican hospital №1 - the National Centre of Medicine (RH№1 –NCM), annual reports of neurologists from all the republic, materials of the Neurologic department of Republican hospital №2 –Medical Emergency Centre, mobile medical inspections over the republic have been analyzed. In the research 113 sick people (54 women and 59 men) with clinical diagnosis CMT from 85 unrelated families have been included. The research has been approved by the local ethical committee FSBE «Yakutsk scientific centre of complex medical problems SD the Russian Academy of Medical Science».

By method of quantitative definition of gene marker*PMP22* (OMIM 601097)intra locus microsatellite alleles a sample of healthy horses of the Yakut population (n=100)has been investigated at the first stage, then 98 accessible DNA samples of CMT patients (36 ones with CMT 1A type and 62 with unknown type) have been studied at the second stage. For the molecular-genetic analysis the genome DNAof CMT patients, having been taken with written informed consent has been used. A population sample of 100 healthy unrelated Yakuts has been given from the «DNA Bank of hereditary and congenital pathology and populations of people RS (Y) ». The

molecular-genetic analysis has been carried out on the basis of the Molecular-genetic laboratory RH№1 - NCM and «Genomic medicine» laboratory of Medical School, North-Eastern Federal University of Ammosov M.K. The genome DNA was extracted from blood leukocytes by the phenol-chloroform method.

The duplication in gene *PMP22* has been searched by means of fragmental analysis on the genetic analyzer ABI Prism 3130 («Applied Biosystems») with the use of the firm-manufacturer's report. The markers *D17S2218*, *D17S2223* and *D17S2229*used in the research (Tab. 1 see) concern a number high polymorphic $(CA)_n$ repetitions closely linked to the gene *PMP22*, applied for searching duplications and carrying out the analysis of coupling of locus 17p11.2 [1,10,11].

The statistical analysis has been conducted with use of SPSS 16.0. The descriptive statistics for quantitative signs is presented in the form of average value and standard deviation, and for qualitative signs is in the form of absolute values, percentage shares. The heterozygosity was counted in %.

**RESULTS AND DISCUSSION**

The general prevalence of Charcot-Marie-Tooth in Republic Sakha (Yakutia) for January, 1st, 2013 has counted 11,8 per 100 thousand population. CMT in our republic is revealed among Yakuts (86 patients), Russians (23 patients), and 1 patient from each ethnic group (Evenk, Moldovian, Nogay, Ukrainian). The share of Yakuts among CMT patients prevailed and has amounted 76 % with prevalence among the Yakut population 18,4 per 100 thousand population.

The diagnosis of Charcot-Marie-Tooth disease 1A type has been detected on the basis of the molecular-genetic analysis of 43 patients from 113, which is 38 % of all CMT forms. The prevalence of CMT 1A type in the republic has amounted 4,5 per 100 thousand population. The genealogical analysis of 43 patients with CMT 1A from 27 unrelated families showed the appearance of autosomal-dominant type of inheritance in 24 families, in 3 families the hereditary load could not to be found out. As regards sexual sign the patients were distributed as follows: men - 25, women – 18; ethnicity: Russian - 15 (35 %), Yakuts - 28 (65 %). Middle age of patients has been 32,2±15,7 years. Middle age at women has been 30,7±15,7 years, at men - 33,4±15,9 years. Statistically significant distinctions between age and sex were not revealed ($p$=0,530). The manifestation middle age has amounted 13,0±9,7 years. The average disease duration has amounted 18,6±13,3 years. As first symptoms patients have noted feet deformation, toe defect, gait worsening, weakness and pain in feet, frequent falling.

In the clinical picture hypo- or areflexia of lower extremities (84 %) and feet deformation of Fridreich's or hollow type (Tab. 2) have been revealed practically at all patients undergone the survey (in 40 cases (93 %)). Also the patients had muscular atrophy of lower and upper extremities

(70 and 49%), sensory defect of polyneuritic type (70%), distal muscular weakness of lower extremities (93 %). The gait worsening in 40 cases was of steppage type (93 %). Scoliosis has been revealed in 19 % of cases.

The clinical manifestation of CMT 1A type can be observed below as an example in the case record of one Yakut family studied by us, the fragment of their family tree is presented on Fig. 1.

During consultation the patient B, 8 years (III-1) was taken into account. In the family of the proband there are 2 sick sibs. The disease had been inherited from the father who had 2 sick sisters and a nephew. The proband felt sick at 7 years, thus the first symptoms were weakness in feet and hands, fatigue; as for the father the disease manifested itself at his 12 years, accompanied by weakness in hands, feet. In the neurologic status of the proband the restriction of back ankle extension, distal muscular weakness of extremities to 3,5 points, feet deformation on Fridreich's type, gait worsening on «steppage» type, decrease of hand and feet sinew reflexes were detected. ENMG revealed the conduction disorder on n. peroneus, tibialis, medianus, ulnaris of both sides at expressed degree of demyelinizing type.

As for her sister the symptoms were noted at 9 years. While examining the gait worsening on «steppage» type, decrease of sinew reflexes, high foot arch, hypesthesia on polyneuritic type, distal hypotrophy of extremities, restriction of back ankle extension were detected. According to electroneuromyography (ENMG) the conduction disorder of hand and feet peripheral nerves, at strongly expressed degree of demyelinizing type.

In brother's (III-3) case the disease debuted at the age of 9 years, in the neurologic status the mild restriction of ankle extension, decrease of achill reflexes, sinewhypesthesia, absence of feet deformation, shin muscular peroneal hypotrophy mainly on the right were found out. ENMG revealed the conduction disorder of hand and feet peripheral nerves at expressed degree on demyelinizing type.

The father's (II-2) inspection has revealed: expressed muscular hypotrophy of lower extremities from the level of low third of hips on type "stork's feet», «steppage» gait, absence of knee and achill reflexes, peroneal muscular weakness to 3 points, feet deformation on Fridreich's type, hypesthesia as so called "socks". In ENMG the conduction disorder on type of demyelinizing neuropathy at expressed degree has been revealed as well.

In the given family the method of fragmental analysis has revealed the duplication of 1,5 Mb in the field of the chromosome 17p11.2-12 in gene *PMP22* at 4 members of the family and 2 relatives. The result of proband's fragmental analysis (Fig. 2) is presented below.

Thus, all patients according to ENMGhad demyelinizing type of sensorial defect that corresponds to CMT 1Atype. In their clinical picture the polyneuropathy syndrome at various

degrees of expressiveness was observed. In the given family the prenatal diagnostics has been conducted, as it revealing fetus mutation, the pregnancy interruption was recommended. The family has been sent to the Republican genetic register of hereditary and congenital pathology, the subsequent long-term supervision will be continued.

**The molecular -genetic analysis**

Till 2011 in the medical-genetic laboratory RH №1-NCM a set «CMT-dup» (Open Company «Center of Molecular genetics», Moscow) was applied for searching duplications in gene *PMP22,* it was followed by electrophoresis in 8 % of polyacrylamide gel (PAG) which in 11 % cases has shown not informative results of the analysis.

In the present research dinucleotide STR-markers *(D17S2218, D17S2223, D17S2229*) have been used with subsequent visualization on the automatic genetic analyzer. At the beginning the fragmental analysis in the sample of healthy Yakut people (n=100) has been conducted and heterozygosity for studied STR-markers (Tab. 3) considered.

The markers*D17S2218* and *D17S2229*had high heterozygosity (on 76 %), i.e. the given markers are considered to be informative in the Yakut population and can be used for revealing duplications. The marker *D17S2223* has appeared less informative (heterozygosity of 49 %) though in other ethnic groups (Caucasian, Afro-American, Asian, Spanish) heterozygosity on the given marker was higher (more than 70 %) [11].

Further by the method of quantitative definition of gene marker *PMP22* intralocus microsatellite alleles 98 accessible samples of DNA with CMT (36 patients with CMT 1A type and 62 with unknown type) had been investigated. 38 patients of 98 patients had the duplication of 1,5 Mb in the field of a chromosome 17p11.2-12 in gene *PMP22* (39 %), in addition revealing two patients with CMT 1A type whose earlier analyses had appeared negative with the use of reagents of the firm set «CMT-dup». The patients who had had not informative results earlier have comprised negative ones.

Also we have considered the quantity of duplications detected for each STR-marker among the patients with CMT 1A type by the method applied (Tab. 4 see). High frequency of detecting the duplication was noted on marker *D17S2229* - 35 of 37, low frequency was on marker *D17S2223* - 14 of 37.

Among the patients with CMT 1A type of the Yakut ethnic group the high frequency (26 of 27) of detecting the duplication on marker *D17S2229*was observed, while the low frequency (9 of 27) on marker *D17S2223* was noted as well.

**Conclusions**

The prevalence of Charcot-Marie-Tooth all types has amounted 11,8 per 100 thousand population, it being the average index all over Russia. Among Yakuts the frequency 18,4 per 100 thousand population is a little higher than the average parameter all over the Russian Federation, but in the ratio with the world data it is the average index. The prevalence CMT 1A type in our republic has amounted 4,5 per 100 thousand population. In the clinical picture the syndrome of polyneuropathy and feet deformation at different degrees of expressiveness was found out.

For detecting the duplication of 1,5 Mb in the field of the chromosome 17p11.2-12 in gene *PMP22* in the Yakut population two informative markers *D17S2218* and *D17S2229*can be offered.

The introduction of molecular-genetic methods in practice of the medical-genetic consultation in the Republic Sakha (Yakutia) has allowed not only to diagnose Charcot-Marie-Tooth disease in families, but also to carry out differential diagnostics of the diseases with similar phenotype.

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Table 1

**Brief Characteristic of Applied Microsatellite Gene Markers *PMP22*[11]**

| Marker | Primeries (direct and reverse) 5'→3' | Size of Alleles (couple of nucleotides) | Number of Alleles |
|---|---|---|---|
| *D17S2218* | F - (FAM)-AAATGCTTGTGGATTAGTTG<br>R-GTGTCTTGGGTACCTTTATGTTTTCTT | 196-230 | 12 |
| *D17S2223* | F - (FAM)-TACAAGAAAGGGAACAAAGC<br>R-GTGTCTTTGAAGAAGCAAGAGACGAGT | 151-179 | 15 |
| *D17S2229* | F - (FAM) -CCCATTCCATAGTCATCAGA<br>R-GTGTCTTTGCCATTTTACCACAAGAGG | 243-269 | 13 |

Table 2

Clinical Symptoms of Patients with CMT 1AType

| Symptoms | Amount of Patients (%) (n=43) |
|---|---|
| Muscular weakness<br>Lower extremities<br>Upper extremities | <br>40 (93)<br>14 (33) |
| Muscular hypotrophy<br>Lower extremities<br>Upper extremities | <br>30 (70)<br>21 (49) |
| Surface sensorial defect of polyneuritic type | 30 (70) |
| Hypo- or areflexia<br>Lower extremities<br>Upper extremities | <br>41 (95)<br>36 (84) |
| Foot deformation | 40 (93) |
| Scoliosis | 8 (19) |
| Steppage | 40 (93) |

Table 3

Heterozygosity of CMT 1A Disease STR-Markersin Various Ethnic Groups

| **Heterozygosity, %** | | | | | |
|---|---|---|---|---|---|
| **Marker** | **Populations** | | | | |
| | **Caucasus [11]** | **Afro-American [11]** | **Asian [11]** | **Spanish [11]** | **Yakut*** |
| *D17S2218* | 87 | 78 | 77 | 69 | 76 |
| *D17S2223* | 71 | 75 | 81 | 71 | 49 |
| *D17S2229* | 93 | 86 | 81 | 71 | 76 |

Note: * - own data

Table 4

Frequency of Duplication Detection for Each Marker among AllPatients with CMT 1AType (n=37) and Separately among Yakuts (n=27)

| **Marker** | **Duplication Detection** | |
|---|---|---|
| | **All patients** | **Yakuts** |
| *D17S2218* | 24/37 | 16/27 |
| *D17S2223* | 14/37 | 9/27 |
| *D17S2229* | 35/37 | 26/27 |

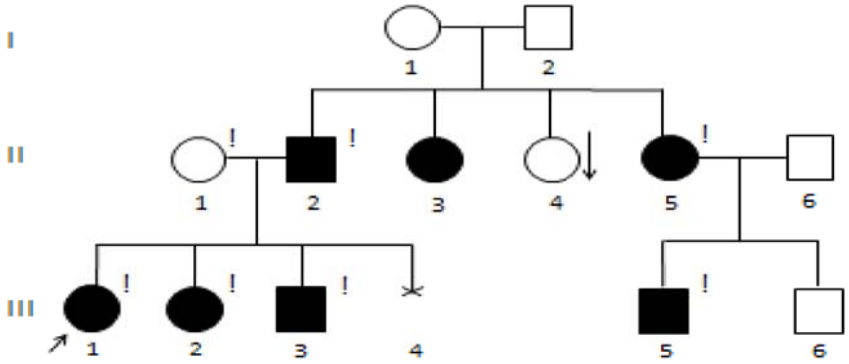


Fig. 1. Fragment of a Yakut family tree (the Ks as the example) with CMTT1A type.

□ – man, ○ – woman; ■, ● – patients with CMT; □, ○ – healthy individuals; x – prenatal diagnostics, ! – personally inspected, ↓ - died. I, II generation – parents, III generation – patients and sibs.

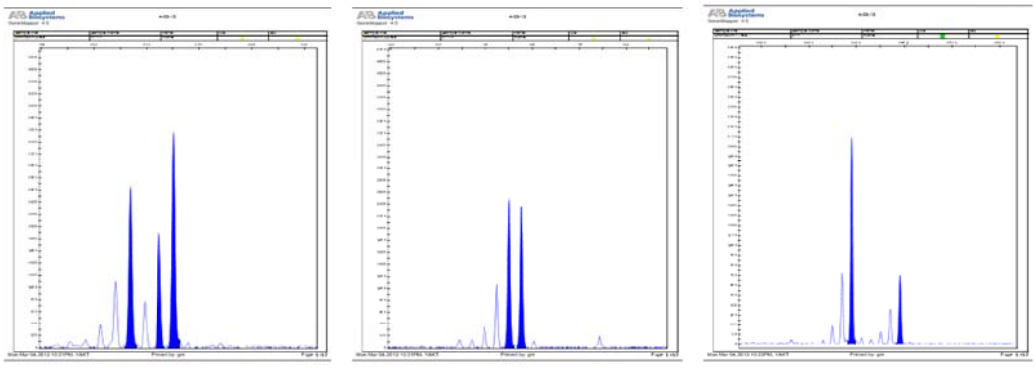

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Fig 2.The result of fragmental analysis of a patient with CMT 1A type: a–duplication on markers *D17S2218* (two normal alleles and one pathologic); b – marker*D17S2223* is normal; b–duplication detection on marker *D17S2229* (double doze effect).

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