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Genetic identification, clinical features and prevalence of Spinocerebellar ataxia type 1 in Sakha Republic (Yakutia)

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Annotation. Over the past several decades, more than 500 cases of Autosomal dominant spinocerebellar ataxia type 1 (SCA1) have been identified in the Republic of Sakha (Yakutia) of North-Eastern Siberia. The disease leads to long-term disability and death, making it a serious public health burden. The prevalence of SCA1 in the indigenous Sakha population has been steadily increasing since the 1970s. It has recently stabilized at a level of 45-53 per 100,000 due to efforts undertaken to limit its further spread.

We describe results of a multi-year study of SCA1 in the Sakha population, including molecular genetics, distribution, clinical, electrophysiological and histopathological characteristics. Each studied patient had a mutation in the coding region of the ATXN1 gene on chromosome 6p22.3. The mutation presents as an uncontrolled increase in the number of trinucleotide CAG repeats from normal 25-32 to 39-72 with a loss of a CAT bridge in the middle of the CAG stretch. The number of continuous CAG triplets in the mutant *ATXN1* gene correlates with the age of onset and the severity of the disease.

The instability of this genomic segment is manifested in meiosis: the number of CAG repeats in a mutant gene increases in transmission from the father by an average of +3.04 repetitions and from the mother by +0.182 repetitions. The total number of repeats transmitted from one generation to another in the Sakha population is on average +1.614, which explains the increase in SCA1 prevalence. Patients from three spatially separate geographic regions of the Republic have the same haplotype, which confirms the origin of the mutation from a common ancestor about 37 generations ago. SCA1 patients in Mongolia, China and the U.S. show a different haplotype. To determine the potential of SCA1 for further spread, the fertility rates of the *ATXN1* mutation carriers were evaluated and the Crow selection index calculated. The resulting score of 0.19 indicates that the mutation has little chance of being eliminated from the population without targeted preventive measures.

Key words: Republic of Sakha (Yakutia), Autosomal dominant spinocerebellar ataxia type 1 (SCA1), ATXN1 gene, trinucleotide repeat expansion.

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Introduction

Autosomal dominant spinocerebellar ataxia type 1 (SCA1, MIM #164400) is a neurodegenerative disease caused by an uncontrolled increase of the number of trinucleotide CAG repeats in the *ATXN1* (Ataxin-1) coding region. To date, more than 30 genetically independent variants of spinocerebellar ataxia have been identified, but among the indigenous Sakha population, SCA1 is the main and probably the only type of inherited autosomal dominant cerebellar ataxia. The diagnosis of SCA was first made in 1971 during the examination of a group of patients in the village of *Abyy* located in the Indigirka Valley, and later in two other regions [1].

The prevalence rate of SCA at the end of 1979 was 384 per 100,000 people in the *Abyysky ulus* and 56 in the *Ust-Aldansky ulus.* Within the following three decades, the SCA1 prevalence in these regions increased to 1182 in *Abyysky* and 273 in *Ust-Aldansky uluses* [2], the highest known for SCA1 and the highest for any chronic neurological disease, including for *Viliuisk encephalomyelitis* in the *Viliuisky ulus* during the time of its maximum [3].

Research directed at the chromosomal localization of the gene responsible for SCA in the Sakha people was undertaken in 1992–93. Initially, a link was established between the putative SCA gene and the genetic loci *D6S274* [4] and *D6S89* [5], which allowed to localize the mutant gene to human chromosome 6p22.3. Collaboration with investigators at the University of Minnesota, who studied affected families from the Netherlands, Germany, England, and South Africa, all with a genetic link to these same loci on chromosome 6p22.3, allowed to identify the ATXN1 mutation found to be responsible for Spinocerebellar ataxia in all studied families [6].

ATXN1, the SCA1 disease gene, contains 10,660 bases in nine exons, of which only two (eighth and ninth) encode *Ataxin1* [7]. The coding region of the *ATXN1* gene contains 6-38 trinucleotide repeats of the type C-A-G and C-A-T. Typically, the CAG path is interrupted by one or more CAT triplets, which serve as "bridges" [8]. *Ataxin1*, respectively, contains a long chain of glutamines. Depending on the length of the polyglutamine tract, normal Ataxin1 consists of 712-825 amino acids [7]. The function of Ataxin1 has not been definitively established, it accumulates in the nucleus of Purkinje cells of the cerebellum and, possibly, participates in the regulation of transcription. Transgenic mice lacking Atxn1 show a moderate deterioration in spatial orientation, but no signs of neurodegeneration [9].

In patients with SCA1, the number of CAG repeats is dramatically increased, and the CAT bridge disappears. The continuous path of the CAG becomes unstable; it can expand or contract during meiosis. The disease develops in individuals who contain 39 or more uninterrupted CAG repeats in the mutant *ATXN1* gene [10]. The number of continuous CAG repeats correlates with the age of SCA1 onset and the severity of the disease [1, 5]. Clinical characteristics of SCA1 correlate with the degree of degeneration of Purkinje cells in the cerebellum and neurons in the cranial nerves' nuclei in the brainstem, and the destruction in the spinocerebellar tracts [11].

Expansion of unstable CAG tracts in other genes cause nine other neurodegenerative diseases that became known as *"polyglutamine expansion diseases"*. This family of diseases includes six types of Autosomal dominant spinocerebellar ataxias (SCA1, 2, 3, 6, 7 and 17) and Huntington's disease.

Patients and methods

Identification of patients. A program of systematic detection, identification and recording of chronic neurological diseases in the Sakha population of Yakutia was launched in 1971 and continued for the next 46 years. The main goal of the program was the identification and registration of patients with neurodegenerative disorders, primarily *Viliuisk encephalomyelitis* (VEM) highly prevalent at that time. In the process, several unrelated chronic neurological diseases were also detected and identified, the Spinocerebellar ataxia among them.

Since then, an effort has been made for the early detection and periodic hospitalization of patients with SCA. Regional neurologists were provided with detailed instructions and supervised by the Encephalitis Department of the Republican Hospital in Yakutsk and traveling groups from the Mos-

cow Institute of Poliomyelitis. Hospitalization for the purpose of a comprehensive evaluation and diagnosis as well as annual re-hospitalization were offered to determine the rate of progression, make treatment adjustments, and establish the level of disability.

In 1994, a *National Electronic Registry of Hereditary Genetic and Congenital Diseases* was set up. A parallel database containing clinical and molecular genetic data was supported at the *Institute of Health, North-Eastern Federal University.* Pedigrees were based on written records or family histories obtained from the patients and their relatives. Studies were conducted in accordance with clinical protocols approved by the Ethics Committee of the Yakutsk Research Center, Siberian Branch of the Russian Academy of Medical Sciences, the Scientific Councils of the North-Eastern Federal University, and the Office of Patient Protection at the US National Institutes of Health. Informed consent was obtained from each participant.

Population statistics was obtained from reports of the *Federal Service for Population Statistics of the Republic of Sakha (Yakutia)* [http://sakha.gks.ru]. The rural Sakha population was relatively stable during the study period.

Diagnostic criteria. Several chronic neurological diseases are common in the Republic of Sakha (Yakutia). In typical cases, SCA1 presents as a chronic neurological disease with signs of progressive cerebellar ataxia of the limbs and trunk, dysarthria, and variably expressed pyramidal symptoms. In most cases, autosomal dominant transmission of the disease can be traced. Genetic analysis demonstrating an increase in the number of CAG triplets and the loss of a CAT bridge in the ATXN1 gene is a convincing evidence for the diagnosis.

DNA studies. Starting in 1994, each new patient suspected of SCA1 has undergone genetic testing. Genetic testing was carried out at the *Clinical Neurogenetics Unit, NINDS, NIH,* and later in the laboratories of the Institute of Health, North-Eastern Federal University, and Yakutsk Research Center, Siberian Branch of the Russian Academy of Medical Sciences. Genomic DNA was isolated from blood lymphocytes using standard phenol-chloroform extraction. A fragment of the *ATXN1* gene containing the region of CAG repeats was amplified by polymerase chain reaction using flanking primers previously described by *Orr et al.* [6]. The amplified fragment was subjected to electrophoresis in a 5% denaturing polyacrylamide gel. Additionally, DNA fragments were cloned into *pBlueScript (Stratagene),* and six clones sequenced on an automated sequencer. In all cases, complete agreement was reached on the number of CAG repeats evaluated by these two methods.

Statistical analysis. Statistical analysis was performed with the use of program packages «*Statistica*» [www.statsoft.com] and «MATLAB» [MathWorks, Inc., MA, USA].

Fig. 1. Three geographic clusters of Spinocerebellar ataxia type 1 in the Republic of Sakha (Yakutia) of North-Eastern Siberia.

Results.
SCA1 geographic distribution

Three clusters of SCA1 have been identified [12]. In accordance with their geographical location, they are designated as the Northern region in the Indigirka Valley corresponding to the *Abyysky* district; the Central region in the Lena-Amga Valley that includes the *Ust-Aldansky* and *Tattinsky* districts; the South-western region in the upper reaches of Viliui and Lena rivers coincides with the territories of *Suntarsky* and *Lensky* districts (Fig. 1).

SCA1 patients registered elsewhere had family connections with people from these three clusters.

Large distances may have contributed to the genetic isolation of populations in the three clusters and the accumulation of SCA1 cases. Genealogical studies in the Northern region have shown that patients were members of three large clans. The disease was traced through 5 generations of one family and 4 generations in two other families. Patients of the Central region come from 8 apparently unrelated families. Social restructuring due to upheavals in the Sakha community (the 1917 Bolshevik revolution, Civil war that followed, and the World War II) accompanied demographic shifts that made it difficult to compile complete genealogical maps. Most patients from the South-western region came from 3 families, in which the disease was present in 3-4 generations. All patients were ethnic Sakha, all born in small villages.

According to the most complete and reliable data from the *National Electronic Registry of Hereditary Genetic and Congenital Diseases* covering 22 years (1994–2016), the number of genetically confirmed cases of SCA1 increased from 101 to 179, reaching prevalence rate of 53 per 100,000 population (Fig. 2). The prevalence rate was estimated based on the number of cases recorded as of January 1 of each year, in relation to the entire rural Sakha population in the corresponding year. Each year, from 4 to 29 patients were newly diagnosed and from 1 to 13 patients died.

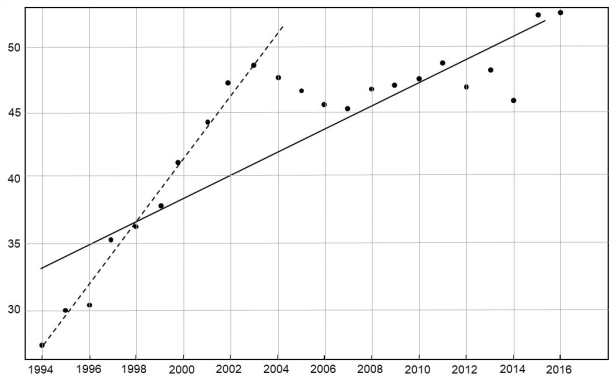

Fig. 2. The prevalence of SCA1 among the rural Sakha population from 1994 to 2016. Dots indicate the prevalence of SCA1 per 100,000 people. The dashed line represents the linear regression slope of +2.37 between 1994 and 2003. The solid line corresponds to the regression slope of +0.89 for the entire period between 1994 and 2016.

Analysis of the long-term prevalence trend of SCA1 shows a sharp increase from 1994 to 2003 with some stabilization after 2004 probably associated with intensive genetic counseling (Mann-Kendall test, $p < 0.0001$) [13].

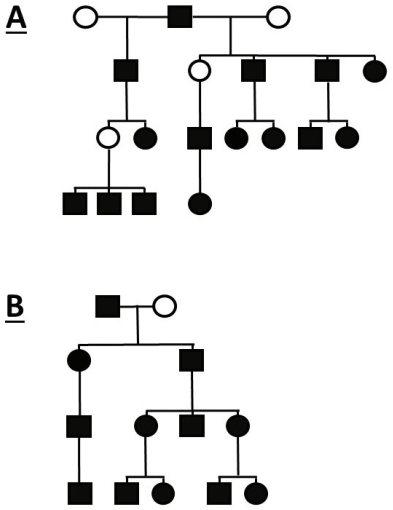

Fig. 3. The pattern of inheritance of Spinocerebellar ataxia type 1 in the Sakha population. A - a family from Abyysky ulus; B – a family from Ust-Aldansky ulus.

Genetic studies

Inheritance pattern. The genealogies of seven large and 35 smaller families included 1,448 people, of whom 225 were patients with SCA1, alive or deceased, and 656 at risk family members. The relationship between patients in two large pedigrees is shown in Fig. 3. In the vast majority of cases, SCA1 is diagnosed in one of the patient's parents, less often in a grandparent or in a more distant relative. Skipping of a generation usually occurs through an unaffected female (Fig. 3A). The pattern of inheritance corresponds to the autosomal dominant type.

ATXN1 gene mutation. The non-mutant ATXN1 gene in the Sakha population contains a chain of 25–32 trinucleotide repeats in which CAG repeat track is interrupted by one and rarely two CAT elements. Of the 88 sequences of normal non-mutant ATXN1, 69% had a bridge with a single CAT triplet. Full information on the configuration of non-mutant trinucleotide tracts is given in Table 1.

Table 1. Configuration of the CAG repeat tract in non-mutant ATXN1 gene in the Sakha population

Конфигурация	Общее число триплетов	Число носителей
11(CAG)-CAT-16(CAG)	28	49
11(CAG)-CAT-17(CAG)	29	7
11(CAG)-CAT-15(CAG)	27	1
12(CAG)-CAT-15(CAG)	28	2
13(CAG)-CAT-12(CAG)	26	2
17(CAG)-CATCAGCAT-10(CAG)	30	10
13(CAG)-CATCAGCAT-10(CAG)	26	4
12(CAG)-CATCAGCAT-15(CAG)	30	3
13(CAG)-CATCAGCAT-13(CAG)	29	3
13(CAG)-CATCAGCAT-15(CAG)	31	2
12(CAG)-CATCAGCAT-10(CAG)	25	1
14(CAG)-CATCAGCAT-15(CAG)	32	1
16(CAG)-CATCAGCAT-10(CAG)	29	2
17(CAG)-CATCAGCAT-9(CAG)	29	1

The *ATXN1* gene mutation was detected in each patient diagnosed with SCA1. The trinucleotide fragment in the mutant *ATXN1* consisted of 39-72 CAG triplets and was devoid of a CAT bridge. The number of repeats varied due to the instability in meiosis. As an example, consider the results of genetic testing in the "R" family with six patients (Fig. 4). The family comes from an area with a high incidence of SCA1. The woman designated "44/30" inherited a mutant gene with 44 CAG repeats from her affected father, but she did not develop SCA1. The woman's husband had SCA1. Each of the four children carries one, and the eldest daughter "50/44" has a mutant gene on both chromosomes.

Instability of the mutant ATXN1 gene. The inherited number of CAG repeats in the mutant *ATXN1* depends on the gender of the transmitting parent (Fig. 5). In 18 of the 22 (82%) studied transmissions from fathers the CAG tract was increased by 1 to 9 repeats (average +3.04), while in 10 of 22 (45%) studied transmissions from the mother, the increase was 1-2 repetitions and in 6 (27%) in a decrease by 1-2 repetitions (average +0.182). The difference between the average of CAG repetitions transmitted from the father and mother is statistically significant (weighted t-test, p = 0.0064). The largest numbers of CAG repeats in our patients (60 and 72) were inherited from fathers. The number of

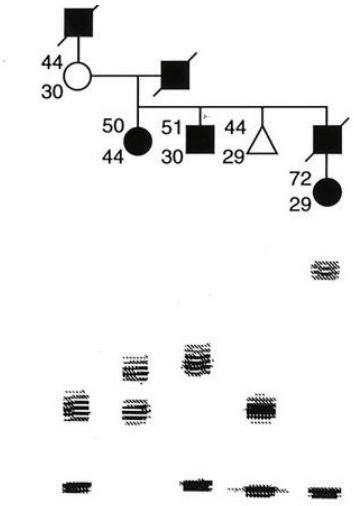

Fig. 4. Analysis of the number of trinucleotide repeats in members of the "R" family using the GeneScan method. The number of trinucleotide repeats is indicated next to the family members' symbols. To determine the number of repeats from several peaks in the densitogram (lower part of the figure), the highest was chosen. Non-mutant *ATXN1* fragments contain 29 or 30 trinucleotide repeats, while mutant fragments contain from 44 to 72 repeats. In patient "50/44", both chromosomes are mutant. Three out of four siblings in the third generation came down with SCA1. A family member indicated by a triangle carries a mutant chromosome, but not yet affected.

Table 2. Microsatellite haplotypes in Sakha, Mongolian, Chinese and U.S. patients with SCA1

Ulus/Country	Number of tested chromosomes	Microsatellites				Haplotype
		D6S260	D6S1605	D6S274	D6S285	
Abyysky	9	15	140	176	3	15-140-176-3
Suntarsky	2	15			3	15----------3
Ust-Aldansky	8	15			3	15----------3
Mongolia	2	7	131	170	3	7-131-170-3
China	4	7			3	7----------3
USA	2	7	140	176	3	7-140-176-4

CAG repeats in the *ATXN1* mutant increases from one generation of the Sakha population to the next by an average of +1.614 CAG repeats. Non-mutant chromosomes are passed from generation to generation without change.

The origin of the ATXN1 mutation in the Sakha population. SCA1 is known worldwide. An attempt was made to establish the origin of the ATXN1 mutation in the Sakha population based on a comparison of haplotypes (Table 2). Mutant chromosomes were examined using informative polymorphic markers *D6S260, D6S1605, D6S274,* and *D6S285.* The results show that patients from the three affected regions of the Republic of Sakha (Yakutia) have the same haplotype, which confirms the origin of the mutant *ATXN1* gene from a common ancestor. The Sakha haplotype differs from the haplotypes in SCA1 patients from Mongolia, China and the U.S. Haplotype-based calculations show that the Sakha mutation may have occurred at least 915 years (37 generations) ago [14-16].

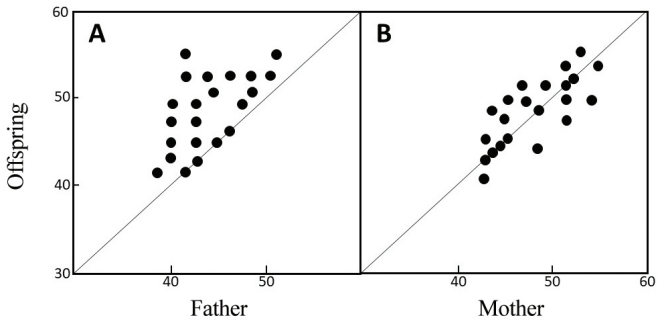

Fig. 5. The number of CAG repeats in the *ATXN1* mutant gene transmitted to offspring from fathers (A) and mothers (B)

Clinical features

Age at onset. The age of SCA1 onset varies from 15 to 57 years and closely correlates with the number of CAG repeats in the coding region of the mutant *ATXN1* gene (multiple correlation coefficient 0.846; p <0.0001). The three youngest patients (two 15-year-olds and a 19-year-old) had the highest number of CAG repeats, 58, 60 and 72, respectively, while patients with the disease onset at a later age, from 45 to 57, had the smallest repeat numbers, from 39 to 45 (Fig. 6). Twenty-three of the

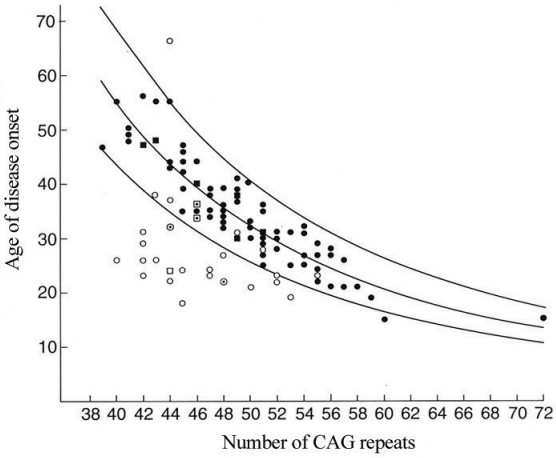

Fig 6. The number of CAG repeats in the mutated *ATXN1* gene of symptomatic (n = 77) individuals relative to the age of disease onset. The middle curve shows the average age of onset, the upper and lower curves correspond to 95% confidence intervals. In both homozygous patients shown here the larger allele is within the 95% interval, while the smaller allele (dot within a circle) is below the lower 95% limit line. The number of CAG repeats in asymptomatic individuals (n = 21) is shown relative to their current age.

26 unaffected carriers of the mutant *ATXN1* gene did not reach the average age of disease onset; two reach critical age, but remained unaffected, and one (a woman) exceeded the 95% limit at the age of 66 years. The average age of onset of the disease decreased in 1994–2003 compared with 1970–1979: 39.0 years against 35.2 years [1].

Clinical description. Observations were carried out in a group of 74 patients who were repeatedly examined throughout their illness [1]. The disease manifests itself gradually with loss of balance when walking - the gait becomes unstable, swaying and legs positioned wide apart. Speech becomes slow and explosive. Early oculomotor signs include nystagmus and hypermetric saccades. As the disease progresses, the frequency of saccades decreases, and nystagmus disappears. Progressive cerebellar deficiency (dysarthria, limb dysmetria, and gait ataxia) was present in all patients, including patients with the smallest number of CAG repeats. Associated symptoms (dysphagia, tongue atrophy, and diffuse skeletal muscle atrophy with fasciculations) were absent or mild in patients with fewer CAG repeats and were significantly more pronounced in patients with larger CAG repeat numbers (slopes from +0.051 to +0.094, all highly significant). In 15 of 22 patients with the number of CAG repeats equal to or greater than 52, lower motor neuron involvement severely complicated the course of illness, and in two patients led to early respiratory death. Pyramidal symptoms — spasticity, hyperreflexia and extensor plantar reactions — were observed in 60% of the examined patients.

As the disease progresses, other signs of cerebellar insufficiency become apparent, such as locomotor asynergy with rhythmic intention tremors, dysdiadochokinesis, and muscle hypotension. Bulbar symptoms, notably dysphagia, appear in relatively late stages of the disease. Atrophy and weakness of skeletal muscles, often with fasciculations, occur in most patients (about 70%) at the late stages. Sensory deficits were uncommon and mild. Relatively rarely, the disease is accompanied by optic nerve atrophy. Memory loss or overt dementia was observed in 10% of patients with rapid disease progression. Respiratory failure develops in the terminal stage and is the cause of death.

Magnetic resonance imaging (MRI) of the brain reveals a slightly atrophic brainstem and inferior olives, in addition to significant cerebellar atrophy and expansion of the fourth ventricle. Electromyograms of patients with widespread diffuse skeletal muscles atrophy with fasciculations showed increased excitability of spinal motor neurons and their possible damage. Electrophysiological studies reveal signs of sensory polyneuropathy. No pathological changes were detected in blood and cerebrospinal fluid tests.

Disease severity and duration. In addition to the early age of disease onset, the rate of disease progression was also faster in patients with more uninterrupted CAG repeats in the ATXN1 gene. Those with 52 or more repeats were significantly disabled by the fifth year of illness: 13 out of 22 were in the terminal stages, and two teenage patients died in the third and sixth years from the onset of the disease. The course of illness in the group of patients with a lower repeat number (39 to 51) was slower. Most developed a pure cerebellar phenotype with no severe complications, and only 8 of 52 patients have become disabled within the 5-year observation. A negative correlation was noted between the number of CAG repeats and the duration of illness [$r = -0.58$ ($p = 0.0008$)], as well as between the number of CAG repeats and the age at death [$r = -0.81$ ($p < 0.001$)].

Homozygosity for ATXN1 mutant. We identified four individuals in which the ATXN1 genes on both chromosomes were mutant with uninterrupted CAG repeat numbers 56/48, 55/48, 54/45 and 50/44. Each homozygous carrier developed SCA1 [18]. The age of disease onset, clinical features and duration of illness in these cases corresponded to those characteristic of the larger of the two CAG tracks.

Neuropathology

One patient with genetically confirmed SCA1 was studied in detail. On macroscopic examination, the cerebellum was significantly atrophied, the bridge was atrophied and wrinkled, and the medulla oblongata was slightly atrophic. Microscopical findings in the cerebellum: an almost complete loss

of Purkinje cells, thinning of white matter, loss of neurons, and intense gliosis in the cerebellar cortex. Significant destruction of neurons in the nuclei of the bridge and relatively moderate losses in the dentate nucleus. Similarly, a moderate loss of neurons in the nucleus of the hypoglossal nerve and lower olives. Degeneration of motor neurons in the upper segments of the spinal cord. Thinning of the lateral pyramidal and spinocerebellar paths.

Differential diagnosis

Two other chronic neurological diseases common in the Republic of Sakha (Yakutia) have some similarities with SCA1. Viliuisk encephalomyelitis in the advanced phase of the disease acquires signs of a chronic neurodegenerative disease. Some patients with chronic VEM have mildly or moderately expressed cerebellar symptoms, but these usually overlap with spasticity and extrapyramidal rigidity. The VEM epidemic has now stopped, some isolated cases with residual non-progressive phenomena still exist [19], but they do not pose problems for differentiation from SCA1.

Autosomal dominant spastic paraplegia was noted in several regions of Yakutia. In one of the families, a mutation in the *DNM2* (dynamin) gene was identified [20]. In the clinical picture, pyramidal and sensory disturbances predominate; cerebellar symptoms are rare. Most importantly, the diagnosis of SCA1 is based on genetic testing.

Factors contributing to the further spread of SCA1 in the Sakha population

Natural selection. We retrospectively estimated the number of children born to patients with SCA1 and compared reproduction rates with those for the entire rural Sakha population. According to the *Federal Service for Population Statistics of the Republic of Sakha (Yakutia),* the birth rate for the entire population of Sakha is estimated at 1.97 children per woman, but data for men is not available. Our estimates of fertility rate in patients with SCA1 show that women carrying a large number of CAG-repeats (56 or more) did not have children, while men had a low fertility rate of 0.83. Thus, long CAG tracks in the mutant *ATXN1* gene are under strong negative evolutionary pressure.

In contrast, carriers of shorter CAG repeat segments are fertile because the onset of the disease is delayed until the end of reproductive age. The birth rate in women with a smaller number of CAG repeats (50 or less) did not differ from the general population: from 1.76 to 2.29 in various pedigrees. For men in this category the fertility rate was from 2.22 to 2.73. Four individuals who were homozygous for the mutant *ATXN1* gene did not have children.

To assess the strength of natural selection and its ability to eradicate SCA1 in the Sakha population, we calculated the selection intensity Crow index [21] using estimates of fertility and child pre-reproductive mortality in mutation-carrying parents (ten mothers and seven fathers) from 17 affected families that were not related to each other. The resulting value of 0.19 is considered low and indicates that the *ATXN1* gene mutation has little chance of being eliminated by natural selection [17].

Medical genetic counseling. Since 2002, genetic counseling of patients with SCA1 and their families has become an important element in serving the SCA1 community [13, 22]. During this time, more than 1,800 genetic tests have been performed [22]. Prenatal testing is offered to individuals at increased risk of transmitting the mutant *ATXN1* gene [23]. If prenatal testing is conducted early enough, and risk of developing SCA1 in adolescence or early adulthood is high, it is recommended that parents receive all the necessary information and the opportunity to make a decision about medical abortion. Of the 48 women who sought help, in 12 the ATXN1 mutation was detected in the fetus. Ten families decided to terminate pregnancy [22].

Discussion

SCAl exists in many diverse ethnic groups, but in most it makes up a relatively small fraction of dominantly inherited cerebellar ataxias [24]. In the Sakha people of Siberia, SCAl is the main and probably the only type of autosomal dominant cerebellar ataxia, which has a high and growing prevalence with a clear tendency to affect young individuals.

Due to the timely patient identification, clinical examination, registration and hospitalization, unique material has been accumulated on the clinical and genetic characteristics of SCA1. The genetic identification of each reported case began in 1994, shortly after the discovery of the *ATXN1* gene. Since 1994, all patients on the SCA1 registry have undergone genetic testing.

SCA 1 in Sakha people has a number of characteristic features compared with this disease in other parts of the world. The SCA1 prevalence rate, which has stabilized in recent years at 45–53 per 100,000 rural population, is at least twenty times higher than the world average, which is estimated at 1–2 per 100,000 [24]. Above-world prevalence rates, but much lower than in the Sakha people, have been reported in two regions of Venezuela [25], the Tamil community of South India [26], Sri Lanka [27] and Miyagi Prefecture in Japan [28]. Compared with other types of SCA, the frequency of SCA1 in the Sakha (Yakut) Republic is closest to the prevalence of SCA2 in the Cuban province of Holguin - 40 per 100,000 [29].

The configuration of the CAG trinucleotide tract in normal *ATXN1* Sakha chromosomes is significantly different from the other populations. 69% of the CAG triplet chains contain a single CAT bridge; in Poland, such triplet structure was found in only 2% of 234 tested chromosomes [30], and in the USA in 9% of 46 [8]. If the critical effect leading to instability were the T-> G substitution (CAT -> CAG), it would have occurred in the Sakha easier than in other populations. Regarding the origin of the pathological *ATXN1* mutation, it was found that patients with SCA1 from different regions of the Sakha (Yakut) Republic have the same historical *ATXN1* mutation that supposedly occurred in a common ancestor about 915 years (37 generations) ago and spread with migrations. The Mongolian, Chinese and American mutant *ATXN1* chromosomes have a different origin.

Data confirm a close inverse correlation between the number of CAG repeats in the uninterrupted CAG tract and the age of the disease onset. This dependence is more pronounced in Sakha than in other populations, reaching a multiple correlation coefficient of 0.846. In other populations, the coefficient varies from 0.5 to 0.7 [31,32]. One of the important clinical characteristics of SCA1 observed in Sakha cases is the presence of pyramidal symptoms in 60% of patients. Pyramidal insufficiency was noted in one third of patients in Italy [33] but was not mentioned in other cohorts [34].

The number of CAG repeats increased significantly in transmission from carrier fathers to their offspring. We also observed an increase in transmission from the mothers, although more modest (average +3.04 repetitions through a male and +0.182 through a female meiosis). In reports from other affected populations, the average number of repeats transmitted from mothers remained unchanged or decreased at an average of - 0.4 [8]; or - 0.5 [10]. The total number of CAG repeats in the mutant *ATXN1* gene increases from one generation to the next by an average of +1.614 repeats, which explains the shift in the incidence of SCA1 to younger age groups. The disease starts at an earlier age, progresses faster and has more severe consequences.

The fertility of female SCA1 patients with CAG repeat numbers of less than 50 does not differ from birth rates of the rural Sakha population; therefore, the *ATXN1* mutation has little chance of being eliminated by natural selection [17]. *Frontali et al.* [35] and *Jodice et al.* [10] came to the same conclusion when studying other populations. The average fertility rate in unaffected female carriers of the ATXN1 mutation is not reduced. F.A. Platonov noted that the age of men at the time of the birth of their first child was 37.4 ± 7.9 years at the beginning of the 20th century but decreased to 23.6 ± 2.2 years by the end of the century. During this same time, the woman's age at the time of the birth of her first child did not change. The decline in the age of men coincided with the transition to a socialist economy, in which young people gave up responsibility for building a house and setting up a farm before marriage. This behavioral shift may have played a role in the transmission of the *ATXN1* gene with longer CAG tracts.

Crow [21] demonstrated that the effectiveness of natural selection in a population can be measured using estimates of differential fertility and differential indicators of infant mortality. The Crow index

in our cohort of SCA1 patients (0.188) is considered very low [36], which supports the conclusion that the mutation has little chance of being eliminated by natural selection. For comparison, in several small Sakha subpopulations the Crow index was 0.462 [37]; or 0.483 [38].

Koneva et al. [39,40] have developed a simulation model that predicts that natural selection may take about 1290 years to eliminate the *ATXN1* mutant chromosomes from the Sakha population, but that this interval can be shortened to 154 years with the introduction of an effective genetic counseling program. Genetic testing of prospective parents and the fetus provides information for family planning and preventing the further spread of this deadly disease [23].

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A note added after this review has been accepted for publication

The authors became aware of a recent publication by Varlamova et al. (2018) on the discovery of Dentatorubral-pallidoluyisian atrophy (DRPLA) in five members of a Sakha family. This disease similarly to SCA1 is associated with an expansion of an uninterrupted CAG repeat in the ATN1 gene. And similarly, ataxia is the dominant clinical feature of DRPLA.

Varlamova MA, Nazarova PS, Ilyinova EA, Pavlova NI, Sidorova OG, Kononova SK, Solovyova NA, Dyakonova AT, Kurtanov XA. Clinical-genealogical and molecular-genetic features of patients with spinocerebellar ataxia type 1 and dentatorubropallidoluyuisian atrophy in Yakutia. Current Problems of Science and Education. 2018; 6.

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