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ORIGINAL ARTICLE

Genetic fitness and selection intensity in a population affected with high-incidence spinocerebellar ataxia type 1

Fedor A. Platonov[1] · Kathrin Tyryshkin[2] · Dmitriy G. Tikhonov[1] · Tatyana S. Neustroyeva[1] · Tatyana M. Sivtseva[1] · Natalya V. Yakovleva[1] · Valerian P. Nikolaev[1] · Oksana G. Sidorova[3] · Sardana K. Kononova[3] · Lev G. Goldfarb[4] · Neil M. Renwick[2]

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Abstract Spinocerebellar ataxia type 1 (SCA1) is the major and likely the only type of autosomal dominant cerebellar ataxia in the Sakha (Yakut) people of Eastern Siberia. The prevalence rate of SCA1 has doubled over the past 21 years peaking at 46 cases per 100,000 rural population. The age at death correlates closely with the number of CAG triplet repeats in the mutant *ATXN1* gene ($r = -0.81$); most patients with low-medium (39–55) repeat numbers survived until the end of reproductive age. The number of CAG repeats expands in meiosis, particularly in paternal transmissions; the average total increase in intergenerational transmissions in our cohort was estimated at 1.6 CAG repeats. The fertility rates of heterozygous carriers of 39–55 CAG repeats in women were no different from those of the general Sakha population. Overall, the survival of mutation carriers through reproductive age, unaltered fertility rates, low childhood mortality in SCA1-affected families, and intergenerational transmission of increasing numbers of CAG repeats in the *ATXN1* gene indicate that SCA1 in the Sakha population will be maintained at high prevalence levels. The low (0.19) Crow's index of total selection intensity in our SCA1 cohort implies that this mutation is unlikely to be eliminated through natural selection alone.

Keywords Spinocerebellar ataxia type 1 · *ATXN1* gene · Northeast Siberia · Sakha (Yakut) population · Genetic fitness · Crow's index

Introduction

Autosomal dominant spinocerebellar ataxia type 1 (SCA1; MIM#164400) is a neurodegenerative disorder caused by a CAG trinucleotide repeat expansion within the coding region of the Ataxin1 (*ATXN1*) gene [1]. The CAG repeat number is unstable; it may expand or contract during meiosis [2, 3]. The number of uninterrupted CAG repeats correlates with the age of SCA1 onset and the severity of illness [4]. In many diverse ethnic groups, SCA1 exists as one of several dominantly inherited forms of cerebellar ataxia [5]. However, in the Sakha people of Eastern Siberia, SCA1 is the major and likely the only type of autosomal dominant cerebellar ataxia. In addition, this variant is notable for its high and increasing prevalence rate and its ever-increasing propensity to affect younger individuals.

SCA1 was identified in 1970 in the northern (Indigirka valley) and later in the southern (Aldan valley) regions of the Sakha Republic [6]. SCA1 prevalence rate in these two regions is the highest in the Sakha (Yakut) Republic [7]. Patients from all affected regions carry an identical haplotype, as determined by typing several intragene variants [8], implying that there has been a single ancestral mutation that occurred no less than 915 years ago and spread through well-documented migrations.

✉ Lev G. Goldfarb
GoldfarbL@ninds.nih.gov

[1] Institute of Health, M.K. Ammosov North-Eastern Federal University, Yakutsk 677010, The Russian Federation

[2] Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON K7L 3N6, Canada

[3] Center for Integrated Medical Research, Academy of Medical Sciences, Yakutsk 677010, The Russian Federation

[4] National Institute of Neurological Disorder and Stoke, NIH, Bethesda, MD 20892, USA

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Each SCA1 patient in the Siberian cohort carries 39 to 72 uninterrupted CAG repeats in the disease chromosome. Normal chromosomes have 25 to 37 CAG repeats interrupted by a bridge of a single CAT triplet in most cases [9]. Meiotic instability of disease chromosomes results in anticipation in which repeat expansion during transmission (particularly paternal transmission) results in an earlier age of SCA1 onset and increased illness severity in successive generations. The rate of increase of the intergenerationally transmitted CAG repeat number and the degree of anticipation may vary between different SCA1 cohorts [3, 4]. Clinical description and the relationship between the CAG repeat number and the phenotypic variability in SCA1 patients have previously been addressed (9).

The longest CAG expansions are under strong negative selection due to reduced genetic fitness. However, mutation carriers with low-median numbers of CAG repeats are mostly fertile because disease onset occurs at the end of reproductive age. In some other CAG expansion disorders, a low-median number of CAG repeats provide fitness advantage that compensates for mortality of the non-fertile carriers of larger poly-CAG stretches. For example, in Machado-Joseph disease (SCA3)-affected women with a moderate number of CAG repeats, genetic fitness was enhanced in comparison with the general population [10].

Changes in SCA1 prevalence rate, patterns of intergenerational transmission of the *ATXN1* mutation, and fertility rates in the affected families should be considered when estimating trends in SCA1 distribution. Here, we examine factors possibly contributing to the preservation and increase of SCA1 morbidity in the Sakha (Yakut) population of Eastern Siberia.

The Sakha (Yakut) population of Eastern Siberia originated from a nomadic Central Asian tribe that migrated to the North Siberian plains 600 to 900 years ago under the pressure of Mongol expansion [11]. By the time of Russian colonization at the beginning of the seventeenth century, the Sakha (also known as Yakut) people lived in a small area in the Lena-Aldan valley (Central Yakutia). The land around these Sakha settlements was occupied by Evenks and Evens reindeer herders and hunters. Being a more civilized and powerful population with a developed economy less dependent on severe climatic conditions, the Sakha assimilated the neighboring indigenous populations and moved to new areas favorable for cattle breeding, including the Indigirka and Viliui valleys [11]. The population grew significantly over the next three centuries, reaching a milestone of 500,000 in 2015. Many Sakha people now live in multi-ethnic cities such as Yakutsk and Aldan. However, the rural population of 350,000 consists almost entirely of Sakha. Our pedigree analysis indicates that SCA1 has long existed in the Lena-Aldan valley, where the Sakha first settled [6]. Studies based on information from family members and church registration data were inadequate for constructing a single pedigree for the entire SCA1-affected cohort because significant parts of the Sakha population migrated from their original settlements to remote areas of the vast Siberian Plateau.

Patients and methods

SCA1 case ascertainment

Starting in 1970, suspected SCA1 cases were identified and examined during systematic ascertainment based on previously developed diagnostic criteria [12]. Early detection and clinical follow-up were accomplished through village-to-village searches and repeated hospitalization. Pedigree charts were constructed based on family histories taken from patients and their relatives. Since 1994, each registered patient underwent genetic testing. Studies were performed by the Institute of Health, M.K. Ammosov North-Eastern Federal University, the Center for Integrated Medical Research, Academy of Medical Sciences, Yakutsk, and the US National Institutes of Health under approved clinical protocols. Informed consent was obtained from each study participant. Registration of SCA1 patients was conducted through the Registry of Hereditary Genetic and Congenital Diseases, Republic of Sakha (Yakutia), and a parallel database containing clinical and genetic data of cases registered between 1994 and the present based on annual reports of district-based neurology services that is maintained at the Institute of Health, North-Eastern Federal University. To estimate annual SCA1 prevalence rates, population statistics were obtained from web-accessible reports of the Federal Government Service on Population Statistics in the Sakha (Yakut) Republic [http://sakha.gks.ru]. Rural Sakha population numbers were relatively stable over the study period.

Genetic analysis

Genomic DNA was extracted from blood lymphocytes using standard phenol-chloroform extraction method. Genetic testing was performed at the Clinical Neurogenetics Unit, NINDS, NIH, and subsequently at the laboratories of the Institute of Health, North-Eastern Federal University, and Center for Integrated Medical Research, Academy of Medical Sciences, Yakutsk. A fragment of the *ATXN1* coding region containing the CAG repeat area was amplified by polymerase chain reaction (PCR) with the use of flanking primers described by Orr et al. [1]. The antisense primer was fluorescently labeled. The PCR-amplified fragment was subjected to electrophoresis in a 5 % denaturing polyacrylamide gel on an automated ABI 373A sequencer.

Fitness and selection intensity studies

We retrospectively estimated the number of children born to registered patients and compared parental reproduction rates to those of the rural Sakha population. To characterize selection intensity, we studied parents from the 17 most recently affected families to determine the number of births and child mortality. The index of selection intensity [13] was calculated using the following formula:

$$I_{tot} = I_m + (I_f/P_s),$$
$$I_m = P_d/P_{s,}$$
$$I_f = V_f/x$$

where I_{tot} is the index of total selection intensity; I_m is the index of differential mortality:

$I_m = P_d/P_s$ in which P_s is the proportion of survivors and P_d the proportion of pre-reproduction deaths (i.e., deaths before 20 years of age); I_f is the index of selection due to fertility, V_f is the variance, and x is the mean of the number of life births per parent at completed fertility (older than 40 and 45 years of age for women and men, respectively). Data processing was performed using a software package for statistical analysis "Statistica" developed by StatSoft [www.statsoft.com] and MATLAB (MathWorks, Inc., MA, USA).

Results

SCA1 prevalence rates in the Sakha population

All SCA1 patients were ethnic Sakha; all were born and lived their entire lives in small villages. The annual number of clinically and genetically confirmed live SCA1 patients slowly increased over time from 101 in 1994 to 161 in 2013. The total number of newly registered SCA1 cases within the 21-year span was 179, and the total number of deceased patients was 116. Prevalence rates were calculated based on the number of SCA1 cases registered by January 1 of each year in relation to the annual total rural population as reported by the Federal Government Service on Population Statistics for the Sakha (Yakut) Republic. Figure 1 illustrates the SCA1 prevalence rates in the rural Sakha population between 1994 and 2014. Annual SCA1 prevalence rate almost doubled during the study period, reaching current levels of 46–48 cases per 100,000. Analysis of the multi-year trend showed a significant increase in the SCA1 prevalence between 1994 and 2003 (Mann-Kendall test, Sen's slope + 2.37 [CI 2.15–1.71], p value <0.0001), with stabilization after 2004 likely resulting from intensive genetic counseling efforts [14].

Disease severity and mortality

Progressive cerebellar deficiency (dysarthria, limb dysmetria, and gait ataxia) was present in all patients. In contrast, life-threatening signs (dysphagia and diffuse skeletal muscle atrophy) were only evident in patients carrying 56–72 CAG repeats. In these patients, lower motor neuron involvement severely complicated the course of illness and led to premature respiratory death, hence the age of death closely correlated with the number of CAG repeats (Pearson correlation coefficient $r = -0.81$; p value <0.001). As many as 95 % of patients with low-median repeat numbers (39–55) died of SCA1 at ages older than 40, indicating that most mutation carriers survive until the end of the reproductive age (Fig. 2). Reliable data for this analysis were available in 48 studied cases.

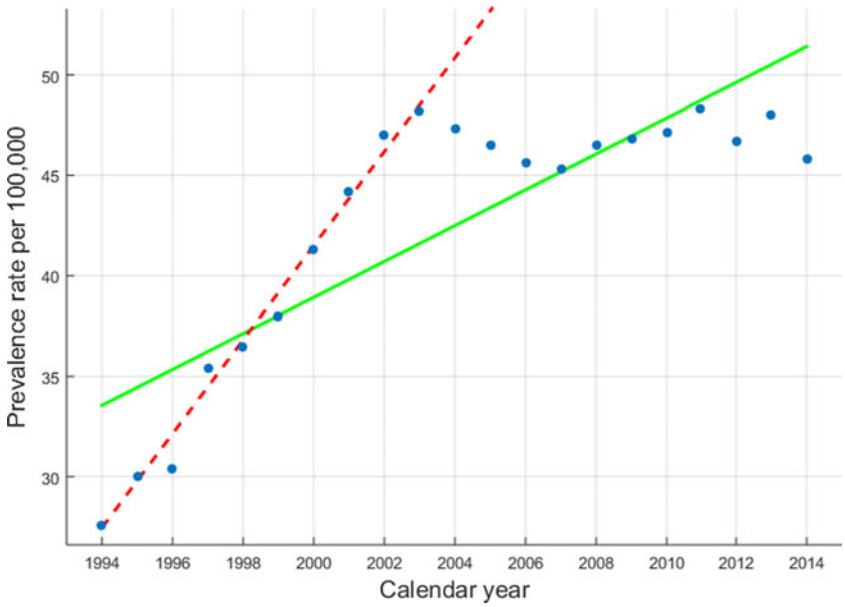

Fig. 1 Increase in annual SCA1 prevalence rate in the rural Sakha population between 1994 and 2014. The *green line* indicates the linear regression slope of +0.89 for prevalence rates between 1994 and 2014. The *red dashed line* indicates the linear regression slope of +2.34 for prevalence rates between 1994 and 2003, the period before the initiation of intensive genetic counseling (Color figure online)

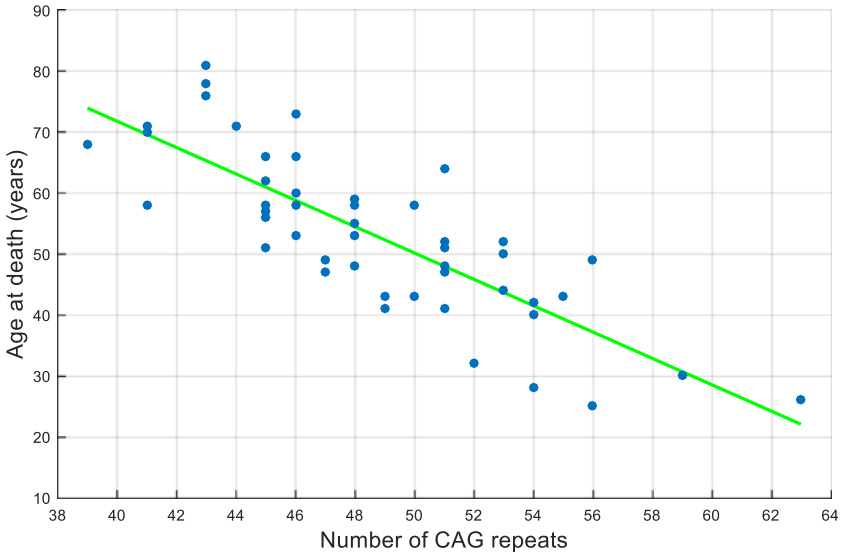

Fig. 2 Negative correlation (Pearson correlation coefficient $r = -0.81$; p value <0.001) between age at death and the number of CAG repeats in the *ATXN1* gene in the Sakha SCA1 cohort. The *green line* indicates the linear regression slope of −2.16, p value <0.0001 (Color figure online)

Intergenerational transmission of unstable disease-associated chromosomes

The inherited number of CAG repeats in the disease chromosomes was dependent on the gender of the transmitting parent (Table 1). Eighteen (82 %) of 22 paternal transmissions resulted in an increase of 1 to 9 (average 3.04) repeats, whereas 10 (45 %) and 6 (27 %) of 22 maternal transmissions respectively resulted in an increase or decrease of 1–2 (average 0.18) transmitted repeats. The difference between the average numbers of CAG repeats contributed through paternal and maternal transmissions was highly significant (weighted two-sample t-test, p value = 0.0064, CI 0.69–5.05). Among our SCA1 patients, chromosomes with the largest number of CAG repeat units were paternally transmitted: the two youngest patients in our series were 15 years old and had the largest number of CAG repeats (60 and 72) inherited from their affected fathers, whereas no CAG repeat expansion was detected in an unaffected control family with normal chromosome architecture (data not shown). Our data indicate that an average increase of 1.61 (weighted standard deviation = 2.764) transmitted CAG repeats should be expected from one generation to the next.

Table 1 Gender-specific parent-to-offspring transmissions of CAG repeats in *ATXN1*-mutation-carrying individuals

Change[a]	−2	−1	0	+1	+2	+3	+4	+5	+6	+9	Weighted mean
Father	0	0	4	4	4	3	2	1	1	3	+3.045
Mother	3	3	6	7	3	0	0	0	0	0	+0.182
Combined	3	3	10	11	7	3	2	1	1	3	+1.614

[a] 0 if the number of CAG repeats was the same in offspring as in the transmitting parent, −1 if it was one repeat shorter, and +1 if one repeat longer

Fertility of ATXN1 mutation carriers

To derive an estimate of natural selection against the *ATXN1* mutation, we compared fertility rates of mutant chromosome carriers with the general population. Fertility rates (number of offspring born to either female or male) were calculated for mutation carriers who either survived beyond reproductive age (40 and 45 years of age for women and men, respectively) or died before reaching these ages. The heterozygous carriers of chromosomes having 55 CAG repeats or less showed average fertility rates of 1.76 to 2.29 for women and 1.1 to 2.73 for men; the average fertility rates for all women and men in our SCA1 cohort were 1.88 and 1.93, respectively (Table 2). The fertility rate for the general Sakha population was estimated at 1.97 children per woman by the Federal Government Service on Population Statistics in the Sakha (Yakut) Republic (no data were available for men).

No significant difference in fertility rate was detected between the SCA1 cohort and the general rural Sakha population (Fisher's exact test, p value = 0.77). No children were born to women carrying 56 or more CAG repeats or to men carrying 58 or more CAG repeats. Four individuals who were homozygous for extended number of CAG repeats did not have children.

Calculation of natural selection intensity

To assess natural selection as a means for eradicating SCA1 in the Sakha Republic, we calculated the Crow index using estimates of differential fertility and child pre-reproductive mortality rates [13]. Table 3 shows the estimated fertility and child mortality rates in mutation-carrying parents (ten mothers and seven fathers) from 17 affected families that were not immediately related to each other according to available pedigree data.

Table 2 Fertility rates of heterozygous carriers of a disease-associated *ATXN1* chromosome

No. of CAG repeats in the *ATXN1* chromosome	Women			Men		
	Number of women	Number of live births	Children per woman	Number of men	Number of live births	Children per man
41–45	21	48	2.29	22	60	2.73
46–50	34	60	1.76	27	60	2.22
51–55	17	35	2.06	20	22	1.1
56–60	2	0	0	6	5	0.83
>60	2	0	0	1	0	0
Total	76	143	1.88	76	147	1.93
General rural Sakha population	76,674	151,203	1.97	nd	nd	nd

nd no data

Discussion

The prevalence rate of SCA1 in the Sakha population of Eastern Siberia (46–48 per 100,000 population) far exceeds the estimated global prevalence rate (1–2 per 100,000 [15]). The prevalence rate increase is accompanied by a shift of morbidity to younger age groups [16]. Notable but considerably lower SCA1 prevalence rates have been reported from two regions in Venezuela [17], the Tamil community of South India [18], Sri Lanka [19], and the Miyagi Prefecture in Japan [20]. Compared to other types of spinocerebellar ataxias, the SCA1 prevalence in Sakha is closest to the SCA2 prevalence rate in a Cuban province of Holguín—40 per 100,000 [21].

Meiotic drive resulting in the increase of CAG repeat number in intergenerational transmissions plays an important role in maintaining the high mutation frequency in the Sakha population. The largest CAG stretches are paternally transmitted. The carriers of 56 or more CAG repeats are childless, suggesting that the largest alleles are lost in each generation [22]. Persistent reproduction of low-medium (39–55) range alleles, mostly through maternal transmissions, supports the preservation of the mutation. On average, combined paternal and maternal transmissions contribute 1.6 CAG repeats to the next generation, indicating that the presence of mutant *ATXN1* is not decreasing and is possibly increasing in the Sakha population.

Selection against deleterious mutations in some conditions may be due to reduced genetic fitness of mutation carriers [23]. In our SCA1 cohort, the average fertility rate of *ATXN1* mutation carriers was not reduced; fitness limitations were only observed in women and men with more than 56 and 58 CAG repeats, respectively. Carriers of low-medium range CAG repeat expansions were only affected later in life and had as many children as women in the general population. It is also worth noting that the age of Sakha males at the time of birth of their first child was 37.4 ± 7.9 years at the beginning of the twentieth century and decreased to 23.6 ± 2.2 years by the end of the century [16]; the age of Sakha females at the time of first birth did not change over the same time period. This decrease in the age of men fathering children coincided with a transition to a socialist way of life in which young men no longer bore responsibility for building a private house and a farm before getting married. This behavioral shift may have played a role in the transmission of the longest CAG stretches.

Natural selection is the main evolutionary force eliminating lethal mutations from affected populations. Crow [13] showed that the effectiveness of natural selection in a population can be measured using estimates of differential fertility and differential child mortality. The proposed index of total selection intensity is also known as the index of opportunity for selection [24]. The Crow's index value in our SCA1 cohort (0.19) is considered very low [25], indicating that the mutation has a low chance of being eliminated through natural selection. By definition, as the index of total selection intensity approaches zero, there will be fewer changes in the genetic makeup of a population [26]. Crow's index has been widely used for quantitative estimation of relative biological fitness of small human populations. In several small Sakha populations, it was estimated at 0.46 [27] or 0.48 [28]. Weak selective pressure in the

Table 3 Crow index calculations for SCA1-affected families

Number of parents	Number of children surviving beyond age 20	Number of children lost before age 20	Child-to-parent ratio	P_s	P_d	x	$I_f = V_f/x^2$	$I_m = P_d/P_s$	$I_{tot} = I_m + (I_f/P_s)$
17	46	1	2.76	0.98	0.02	1.25	0.16	0.02	0.19

I_{tot} index of total selection intensity; I_m index of differential mortality, $I_m = P_d/P_s$ in which P_s is the proportion of survivors and P_d the proportion of premature deaths; I_f index of selection due to fertility, $I_f = V_f/x^2$ in which V_f is the variance and x the mean number of life births per parent

SCA1 cohort indicates that the frequency of a genetic variant may remain unchanged for a long time. Koneva et al. [7] developed a simulation model of SCA1 distribution in the Sakha population, predicting that it may take about 1290 years for natural selection to eliminate the mutant *ATXN1* chromosomes; this interval could be shortened to 154 years with the introduction of an effective genetic counseling program.

Conclusion

The prevalence rate of SCA1 in the Sakha population reached its highest recorded level of 48 cases per 100,000 in 2013. Most patients with low-medium CAG repeat numbers (39–55) survived through reproductive age, and their genetic fitness was not reduced. The number of CAG repeats expands in meiosis, particularly in paternal transmissions; the average increase in intergenerational transmissions in our cohort was estimated at 1.6 CAG repeats. Reproduction of chromosomes with low-medium CAG repeat numbers preserves the mutation in successive generations whereas chromosomes containing elongated CAG stretches are generated anew. The unaltered fertility rate and lack of effect on child health and development in SCA1-affected families contribute to the preservation of the mutant gene and accumulation of SCA1 in Sakha population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights and informed consent We complied with the ethical principles regarding research involving human subjects set forth in the Belmont Report and the Declaration of Helsinki, and informed consent has been obtained from each study participant.

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