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Population genetics of spinocerebellar ataxias caused by polyglutamine expansions

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Hereditary disorders of the neuronal system are some of the most important problems of medicine in the XXI century. The most interesting representatives of this group are highly prevalent polyglutamine spinocerebellar ataxias (SCAs). It has a basement for quick progression of expansion among different groups all over the World. These diseases are SCA1, 2, 3, 6, 7 and 17, which phenotypically belong to one group due to similarities in clinics and genetics. The substrate of these genetic conditions is CAG trinucleotide repeat of Ataxin genes which may expand in the course of reproduction. For this reason a characteristic feature of these diseases is not only an increase in patient numbers, but also a qualitative change in the progression of their neurological symptoms. All these aspects are reflected in the structure of the incidence of polyglutamine SCAs, both at the global level and at the level of individual population groups. However, most scientific reports that describe the population genetics of polyglutamine SCAs are limited to quantitative indicators of a specific condition in a certain area, while the history of the occurrence and principles of the distribution of polyglutamine SCAs are poorly understood. This prevents long-term predictions of the dynamics of the disease and development of strategies for controlling the spread of mutations in the populations. In this paper we make a detailed analysis of the polyglutamine SCAs population genetics, both in the whole world and specifically in the Russian Federation. We note that for a better analysis it would be necessary to cover a wider range of populations in Africa, Asia and South America, which will be possible with the development of new methods for molecular genetics. Development of new methods of detection of polyglutamine SCAs will allow the scientists to better understand how they lead to the brain disease, the means of their spread in the population and to develop better methods for therapy and prevention of these diseases.
Key words: spinocerebellar ataxia; polyglutamine diseases; population genetics; epidemiology.

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Популяционная генетика полиглутаминовых спиноцеребеллярных атаксий

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Наследственные заболевания нервной системы – одна из наиболее актуальных проблем медицины XXI века. Особо выделяются те, которые доминируют в этой группе. К таким заболеваниям, безусловно, можно отнести полиглутаминовые спиноцеребеллярные атаксии (СЦА), имеющие в своей основе молекулярные механизмы быстро прогрессирующей экспансии среди различных групп населения нашей планеты. Это СЦА1, 2, 3, 6, 7 и 17, фенотипически объединенные в одну группу по принципу развития мозжечковой атаксии вследствие специфических генетических причин. Субстратом данных генетических заболеваний является ЦАГ тринуклеотидная

последовательность (цитозин-аденин-гуанин), которая имеет тенденцию к увеличению при передаче генома последующим поколениям. Поэтому характерная особенность этих заболеваний – не только количественное увеличение больных, но и качественное изменение течения их неврологической симптоматики. Все это отражается в структуре заболеваемости полиглутаминовыми СЦА как на глобальном общемировом уровне, так и на уровне отдельных групп населения конкретных регионов. Однако большинство работ, посвященных популяционной генетике полиглутаминовых СЦА, ограничиваются количественными показателями конкретной нозологии на определенной территории, тогда как история возникновения и принципы распространения полиглутаминовых СЦА на сегодняшний день исследованы недостаточно хорошо. Это не позволяет делать долгосрочные прогнозы относительно динамики в последующих поколениях и управлять мутагенным процессом. В настоящей работе представлен детальный анализ популяционной генетики полиглутаминовых СЦА, выведены общие генетические и частные закономерности их развития и особенности популяционной динамики в мире и в Российской Федерации. Обозначены проблемы в исследовании и выявлении таких заболеваний. Для лучшего понимания необходимо охватить широкий пласт популяций Африки, Азии и Южной Америки, что будет возможно при развитии новых методов молекулярной генетики. Такой подход к исследованию полиглутаминовых СЦА позволяет обозначить их место в контексте генетических заболеваний головного мозга и определить особенности распространения и методов генетической профилактики.
Ключевые слова: спиноцеребеллярная атаксия; полиглутаминовые заболевания; популяционная генетика; эпидемиология.

Introduction

In 1991 a new type of mutations in the human genome was discovered, the so-called "dynamic mutations". These mutations cause an increase in the number of copies (expansion) of the simple repeating sequences (Kremer et al., 1991; Warren 1996). As was revealed later, there are numerous simple (CAG, GCG, GCC, GAA, CTG) (Verkerk et al., 1991; Brook et al., 1992; Matilla et al., 1993; Kawaguchi et al., 1994; Koide et al., 1994; Gedeon et al., 1995; Campuzano et al., 1996; David et al., 1997; Zhuchenko et al., 1997; Babovic-Vuksanovic et al., 1998; Brais et al., 1998; Xiang et al., 1998; Vincent et al., 2000; O'Hearn et al., 2001), and more complex repetitive sequences (CTGG, ATTCT, CCCCGCCCCGCG) (Lalioti et al., 1997; Liquori et al., 2001; Potaman et al., 2003). The most common and heterogeneous group of such diseases is the group caused by expansion of CAG triplet in relevant genes (Table 1). CAG encodes the amino acid glutamine, so these diseases are called "polyglutamine" (Zoghby, Orr, 1999).

Today, we know of at list nine such conditions. The first one, which was described in 1991, linked to CAG expansion and causing the progressing degeneration of motor neurons, was the spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease (La Spada et al., 1991). Subsequently also this pathological mechanism has been found in eight other diseases, including Huntington's disease (HD) in the huntingtin gene, dentato-rubral-pallido-luysian atrophy (DRPLA or Haw River syndrome) in the *ATN1* gene, and six types of spinocerebellar ataxias (SCA1, 2, 3, 6, 7, and 17) (Gardian et al., 2005).

Among all polyglutamine diseases there, SCAs have the most similar pathophysiology, progression and clinical signs. Their genetics, however, is not identical (see Table 1).

Features of mutagenesis in polyglutamine SCA progression

Mechanisms of mutagenic process are dramatically different from those of the static mutations. This explains the dominance of polyglutamine SCAs over SCAs caused by static mutations. In comparison to point mutations, which occur spontaneously and stochastically, dynamic mutations have a substrate, the CAG sequence, which initially is repeated only several times (Dunnen, 2017). CAG sequence expansion usually takes place during mitosis of somatic and germ cells. Trinucleotide repeat expansion occurs by replication-dependent (Kovtun, McMurray, 2001), and reparation-dependent (Kovtun et al., 2007) mechanisms. These disturbances are the cause of the phenomenon called "anticipation", when the disease occurs progressively earlier and is more severe in subsequent generations. It was discovered that, the longer the allele is, the more unstable it becomes. The average number of CAG repeats expanded during reproduction depends on the SCA type (from +0.5 CAG repeats in SCA3 to +12 CAG repeats in SCA7) (Stevanin et al., 2000). Paternal alleles are more unstable during transmission which is probably due to a larger number of mitotic divisions during sperm cell maturation compared to oocytes during gametogenesis. However, it could also be linked with decreases in repair DNA protein concentration and activity (Pearson et al., 2005).

The prevalence of polyglutamine SCAs

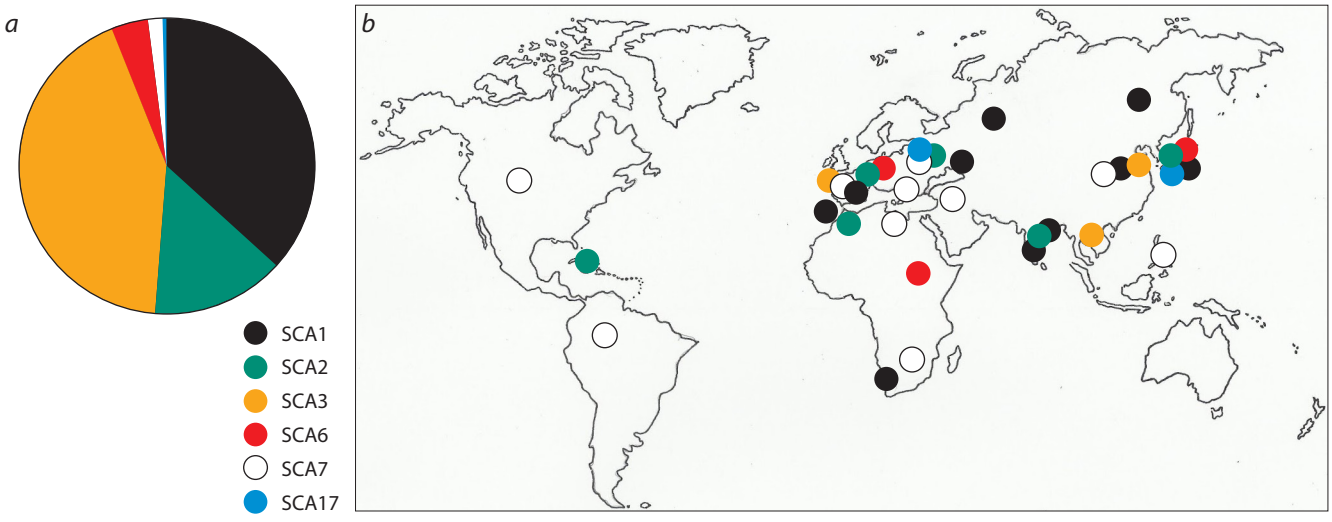
The total morbidity of polyglutamine SCAs is dramatically variable and varies around 1–9 per 100.000 with more accurate accounts being 4–5 per 100.000.

SCA1 is observed, approximately, at a frequency of 1–2 people per 100.000 of "general" population (Manto, 2005). SCA2 has been revealed in 14 % of cases of all SCAs, which makes up about 0.6 per 100.000 population (Cancel et al., 1997; Geschwind et al., 1997a; Riess et al., 1997). SCA3 at some areas is the most common autosomal dominant SCA (Schols et al., 2004; Bauer et al., 2005). The frequency of SCA3 is ~1.5–2 persons per 100.000 population (van de Warrenburg et al., 2002). The world-wide incidence of SCA6 comes near 0.02–0.31 per 100.000 population (Geschwind et al., 1997b; Ikeuchi et al., 1997; Matsumura et al., 1997; Matsuyama et al., 1997; Riess et al., 1997; Stevanin et al., 1997; Schöls et al., 1998; Pujana et al., 1999; Jiang et al., 2005). The incidence of SCA7 in several studies was 2 % of all SCAs, but according to the most accurate calculations it is 0.05–0.2 (an average 0.08) per 100.000 (Filla et al., 2000; Storey et al., 2000). Less than 100 families with SCA17 have been described to date (~0.0015 per 100.000) (Maruyama et al., 2002; Alendar et al., 2004; Craig et al., 2005) (Figure, *a*).

Overall, about 60 % of all clinical SCAs are polyglutamine SCAs, while the other identified and accurately diagnosed forms comprise less than 5 %. It is therefore important to note

Table 1. Molecular characteristics of polyglutamine SCAs

Disease	Locus	Gene	Protein	Polyglutamine chain	
				Norma	Pathology
SCA1	6p23	*Atxn1*	Ataxin-1	6–39	41–83
SCA2	12q24	*Atxn2*	Ataxin-2	14–32	34–77
SCA3	14q24-q31	*Atxn3*	Ataxin-3	12–40	55–86
SCA6	19p13	*CACNA1A*	α_{1A} P/Q Ca^{2+} channel	4–18	21–33
SCA7	3p21–p12	*Atxn7*	Ataxin-7	7–18	37–306
SCA17	6q27	*TBP*	TATA-box-binding protein	25–43	45–63



Worldwide distribution of polyglutamine SCAs.

a – the pie chart shows the percentage ratio of each polyglutamine SCA relative to the total number calculated per 100.000 population (SCA17 is only 0.037 % of the total, this value is not seen in the graph); *b* – on the World map is shown the place of occurrence of corresponding disease haplotype (black and white circles).

that 35–40 % of SCAs have no established genetic base and are only characterized by the phenotype (Bird, 1998; Jayadev, Bird, 2013). At the same time, among polyglutamine SCAs, SCA1 and SCA3 comprise 2/3 of all registered cases (37 and 42 % respectively) (see Figure, *a*).

Polyglutamine SCAs prevalence rate in Russia

Research into polyglutamine diseases in Russia has been carried out for over 20 years. The prevalence of polyglutamine SCAs in Russia is similar to those in the European populations, but there are also differences. From 105 Russian families (excepting the Yakut population) with polyglutamine diseases, SCA1, 2, 3, 6, 7 and 17 was diagnosed in 61 families. The prevalence of SCAs are: SCA1, 28 families (46 %); SCA2, 21 (34.4 %); SCA3, 7 (11.5 %); SCA6, 1 family; and SCA7, 1 family (per 1.6 %). SCA17 was found in 3 families (Klyushnikov et al., 2016, 2017). Thus, characteristic in the Russian population is a low incidence of SCA3, while in populations of the USA and Japan it is the most frequent pathology (Klyushnikov et al., 2008). Notably, the prevalence of SCA17 is very high in comparison to the distribution in global population.

It is interesting that the preponderance of SCA1 over SCA3 is common in yet another population of the Eastern Europe, Poland. The morbidity of polyglutamine SCAs in Polish population is as follows: SCA1, 83.6 %; SCA2, 13.9 %; SCA3, 0.6 %; and SCA17, 1.8 % (Krysa et al., 2016).

Genetic aspects of the origin and expansion of polyglutamine SCAs genesis

Advancements in population genetics and paleogenetics have allowed scientists to trace when polyglutamine SCAs appeared in the human population. The mutation of a gene is quite an unusual phenomenon, therefore such diseases are characterized by the presence of the founder, the person who for the first time gained a certain mutation and became the origin of the unique genetic profile called “haplotype”. Analyses of haplotypes help reveal the dynamics, common factors that affect the disease and predict the development of this pathology in the future. In polyglutamine SCAs, several haplotypes of founders were traced, with at least 2–3 separate haplotypes in each population (Lund et al., 2001; Bettencourt, Lima, 2011) (see Figure, *b* and Table 2). Usually, the mytation rate is higher and/or the mutation is older when it can be detected in wider populations or when it can be detected with a higher incidence (Lund et al., 2000; Bettencourt, Lima, 2011). However, due to the “anticipation” phenomenon, these two factors are mutually

Table 2. Worldwide distribution of poliglutamine SCAs

Mutation rate	SCA	Haplotype	Place of inhabitance	References
Slow (time of origin 80.000 years ago and later)	SCA3	Asiatic	Taiwan, India, Japan, Australia	Gaspar et al., 2001; Verbeek et al., 2004
		Portuguese (global distribution due to the great geographical discoveries)	North America, Germany, France, Portugal, Brazil, India, China, Australia	Bettencourt, Lima, 2011; Martins et al., 2012
		Cambodian (possibly a variation of the Portuguese haplotype)	Cambodia, United States	Jayadev et al., 2006
	SCA6	Paleolithic (before the division of humanity into races)	England, Japan, Brazil, Finland	Craig et al., 2008
		German	North Rhine-Westphalia	Dichgans et al., 1999
		Japanese	Tottori Prefecture	Mori et al., 2001
Fast (time of origin 900 years ago and later)	SCA1	Japanese	Miyagi and Yamagata Prefectures	Wakisaka et al., 1995; Zhou et al., 2001
		Yakut	Russia (Yakutia), China	Gouriev, 2004; Osakovsky et al., 2004; Zhou et al., 2001
		Hindustani	India (Bihar)	Mittal et al., 2005; Sinha et al., 2004
		Tamil	India (Tamil Nadu)	Mittal et al., 2005; Rengaraj et al., 2005
		Western Cape (3 haplotype may be present at once)	South Africa (Western Cape)	Ramesar et al., 1997
		Spanish	Girona, Catalonia	Pujana et al., 1999
		Italian	Southern Italy	Jodice et al., 1993
		Eastern European	Russia, Ukraine, Belarus	Popova et al., 2001
		Bashkir	Republic of Bashkiria	»
		Polish	Wielkopolska and Lodz Voivodeship	Krysa et al., 2016
	SCA2	Western European	Germany, France	Didierjean et al., 1999
		Pan-European	France, Germany, Serbia	»
		North African	Morocco, Libya	»
		Caribbean	Jamaica, Cuba	»
		Indian	India (Bihar)	Choudhry et al., 2001
		Japanese	Gunma Prefecture	Mizushima et al., 1998
	SCA7	Haplotype of Continental Europe	Belgium, Finland, France, Germany, Sweden and UK	Stevanin et al., 1999
		Italian	Italy	»
		Asiatic	Korea and Philippines	»
		Middle Eastern	Israel	»
		Anglo-Saxon	UK, USA	»
		North African	Algeria, Morocco, Tunisia	»
		South American	Brazil	»
		Scandinavian	Sweden	Jonasson et al., 2000
		South African	South African	Greenberg et al., 2006
	SCA17	Japanese	Niigata Prefecture	Koide et al., 1999
		German (high instability of CAG repeats)	Northern Germany	Zühlke et al., 2005
		German (low instability of CAG repeats)	Germany	De Michele et al., 2003; Zühlke et al., 2003

exclusive in polyglutamine SCAs. This conclusion could be suspected by comparing the haplotype numbers and SCA time of origin (see Table 2).

According to the mutation speed, age of clinical presentation and time of origin, polyglutamine SCAs can be divided conditionally into two groups. The first comprises diseases with early presentation and low speed of mutations, SCA3 and SCA6. 2–3 haplotypes are known for each polyglutamine disease.

In the case of SCA6, the size of the area occupied by the diseased population directly correlates with the time of its origin. The worldwide distribution of this pathology charac-

terized by a very low degree of mutation can be linked to the presence of a Paleolithic haplotype which arose before the division of humanity into races (about 80.000 years ago) (Craig et al., 2008). The Asiatic haplotype of SCA3 arose in the prehistoric period (about 7.000 years ago). People with this haplotype live in South and Southeast Asia, and also in northeastern part of Australia (Martins et al., 2012). However, the worldwide distribution of SCA3 is explained differently. The Portuguese haplotype arose ~1400 years ago and was local until the era of great geographical discoveries (Bettencourt, Lima, 2011). The active exploration of the World Ocean by the Portuguese resulted in this haplotype quickly spreading to the countries of Asia and the New World (Martins et al., 2012). While these haplotypes make a significant contribution to the incidence of SCA3 and SCA6, there are also "younger" local haplotypes all over the World (Dichgans et al., 1999; Mori et al., 2001; Jayadev et al., 2006).

The widespread distribution of SCA1, SCA2, SCA7 and SCA17 in the world population is due to a different reason than SCA3, SCA6. These diseases are characterized by a high level of mutations. The mutations that cause these diseases are relatively young: in most cases, they are present only in 1–20 generations and are common within various ethnic groups. Patients with these polyglutamine SCAs exhibit numerous haplotypes, in some cases these are just individual haplotypes in a single population.

SCA1 is distributed worldwide, however, the main proportion are local haplotypes. It could be seen clearly in populations of islands and remote areas with low migration rates (Wakisaka et al., 1995; Wadia et al., 1998; Sinha et al., 2004; Mittal et al., 2005; Rengaraj et al., 2005). In other regions, such as Eastern Europe, migration was always high and it lead to the spread of SCA1 to different parts of the Eurasian continent. The prevalence of SCA1 in the Russian population is due to the presence of three specific haplotypes (Eastern European, Yakut and Bashkir) (Popova et al., 2001; Gouriev, 2004).

The same tendency could be seen in other polyglutamine SCAs with high mutation rates (SCA2, SCA7 and SCA17). Here there is a large number of "young" haplotypes all over the World (Mizushima et al., 1998; Didierjean et al., 1999; Koide et al., 1999; Stevanin et al., 1999; Jonasson et al., 2000; Choudhry et al., 2001; De Michele et al., 2003; Zühlke et al., 2003, 2005; Greenberg et al., 2006). There are huge "white spots" on the World Map, which may contain a large number of yet unknown haplotypes of the polyglutamine SCAs with unique genetic signatures and clinical features. Within Africa, the northern and southern parts are relatively well studied, and several haplotypes were found among peoples living in these territories (Ramesar et al., 1997; Stevanin et al., 1999; Greenberg et al., 2006), whereas the central part of Africa remains completely unexplored.

The data obtained by Japanese researchers confirm that the incidence of polyglutamine SCA is not static, it is a dynamic process that continues and changes continuously. For example, a Japanese girl with SCA17 from Niigata Prefecture was described who had a *de novo* duplication from her father's allele (Koide et al., 1999). Therefore, she could be "founder" of a new haplotype.

The study of the haplotypes of polyglutamine SCA is important for practical medicine. In the German population, there are two haplotypes of SCA17. The first haplotype is characterized by a high instability of CAG repeats during transmission (Zühlke et al., 2005). The second haplotype is more stable (De Michele et al., 2003; Zühlke et al., 2003). For this reason, the identification of a haplotype is important not only for assessing the incidence in a single population, but also for predicting the course of the disease and for medical-genetic counseling of patients.

Isolation as a factor in the incidence of polyglutamine SCAs enhancement

Isolation is a strong factor contributing to polyglutamine SCAs. Isolation could be seen not only in areas with a low migration history due to the remoteness of the place or ethnic characteristics, but also it could be linked to traditions leading to closely related marriages (Dedov et al., 2004; Maximova et al., 2008). The most vivid example of natural isolation is the population of the small island named Flores of the Azores archipelago, where there is the highest incidence of SCA3 in the world, 1 of 140 people (Lima et al., 1998). Another striking case of natural isolation is the larger Yakut population, where the incidence of SCA1 is about 46 cases per 100 thousand population (Platonov et al., 2016). Until the XX century, the population of the Japanese islands remained in relative isolation from other peoples. Confirmation of this can be found in the official data of SCA1 incidence in Miyagi and Yamagata Prefectures where the migration rate is the lowest in Japan (Wakisaka et al., 1995). However, geographical isolation is always a relative phenomenon. Thus, in China, not only Chinese but also Yakut and Japanese haplotypes have been reported (Zhou et al., 2001).

However, a high level of genetic isolation of a certain group of people may be due not only to geographical factors. The ethological (cultural, ethnic etc.) isolation of small populations in India, who obey a cast system, also leads to impressive consequences. Thus, SCA1, which is uncharacteristic of India, is observed in Tamil families living exclusively in two villages of Rajapalayam and Kottamedu of Tamil Nadu state, with an incidence of 1 SCA1 patient per 15 healthy residents (Rengaraj et al., 2005). In general, isolation has no global effect on morbidity (Mori et al., 2001), but it is a decisive factor for a specific group of people who live for a long time in the same territory.

Conclusions

Polyglutamine SCAs have appeared a long time ago and are spread all over the World. Insufficient information on polyglutamine SCAs does not allow accurate determination of the incidence and prevalence among some population groups. Extensive regions such as Africa, India, Southeast Asia, remain virtually unexplored in terms of these diseases. However, analysis of available data from population genetics reveals a number of features of polyglutamine SCAs. The common features with other hereditary diseases are the presence of the founder, the dependence of the prevalence on the age of the mutation and the frequency of mutagenesis, as well as the prevalence of SCAs in isolated populations. The specifics of SCAs is determined by their mechanism since they occur not due to spontaneous mutagenesis but result from duplications of pre-existing CAG repeats. This mechanism explains the

prevalence of polyglutamine SCAs over others SCAs in the global population, and also the phenomenon of "anticipation". The anticipation needs to be taken into account in order to explain the dependence of the time of presentation of the disease on the rate of mutation.

One may speculate that 5–7 thousand years ago mainly diseases with a low mutation rate (*SCA3* and *SCA6*) were present, since types with high rates (*SCA1*, *SCA2*, *SCA7* and *SCA17*) lead to a rapid elongation of CAG repeats and the manifestation of the disease at younger ages in subsequent generations, which inevitably leads to the exclusion of the affected individuals from the process of reproduction.

The study of polyglutamine SCAs from the point of view of population genetics makes it possible to better determine their place in the context of genetic diseases of the brain and to understand the biological, ethnic and social features of these diseases. The development of molecular genetics will allow the scientists to cover, in the future, a wide range of populations in Africa, Asia and South America, which might not only change our understanding of the time and pattern of distribution of polyglutamine SCAs, but also reveal new mechanisms of the mutation process and disease progression.

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