

Population genetics of spinocerebellar ataxias caused by polyglutamine expansions

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Abstract:

Hereditary disorders of neuronal system are one of the most actual problems of medicine of 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 patients 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 which describe the population genetics of polyglutamine SCAs are limited to quantitative indicators of a specific condition in a certain area, whereas 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 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 the new methods of molecular genetics. Development of new methods of detection of polyglutamine SCAs will allow 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.

Популяционная генетика полиглутаминовых спиноцеребеллярных атаксий

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Аннотация:

Наследственные заболевания нервной системы являются одной из наиболее актуальных проблем медицины XXI века. Среди них особо выделяются те, которые доминируют в этой группе. К таким заболеваниям, безусловно, можно отнести полиглутаминовые спиноцеребеллярные атаксии (СЦА), которые имеют в своей основе молекулярные механизмы быстро прогрессирующей экспансии среди различных групп населения нашей планеты. Это СЦА1, 2, 3, 6, 7 и 17, фенотипически объединённые в одну группу по принципу развития мозжечковой атаксии вследствие специфических генетических причин. Субстратом данных генетических заболеваний является ЦАГ тринуклеотидная цепочка, которая имеет тенденцию к увеличению при передаче генома последующим поколениям. Поэтому характерной особенностью данных заболеваний является не только количественное увеличение больных, но и качественное изменение течения их

неврологической симптоматики. Всё это отражается в структуре заболеваемости полиглутаминовыми СЦА, как на глобальном общемировом уровне, так и на уровне отдельных групп населения конкретных регионов. Однако, большинство работ, посвящённых популяционной генетике полиглутаминовых СЦА, ограничиваются количественными показателями конкретной нозологии на определённой 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 данной работе представлен детальный анализ популяционной генетики полиглутаминовых СЦА, выведены общие генетические и частные закономерности их развития и особенности популяционной динамики в Мире и отдельно в Российской Федерации. Также обозначены проблемы в исследовании и выявлении данных заболеваний. Для лучшего понимания необходимо охватить широкий пласт популяций Африки, Азии и Южной Америки, что будет возможным 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 её распространения и методов генетической профилактики.

Ключевые слова: Спиноцеребеллярная атаксия, полиглутаминовые заболевания, популяционная генетика, эпидемиология.

Introduction:

In 1991 a new type of mutations in 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 it was revealed later, there are numerous simple (CAG, GCG, GCC, GAA, CTG) (Verkerk et al., 1991; Brook et al., 1992; Marcy et al., 1993; 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, CCCC GCCCGCG) (Laloti 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 Huntingtin gene, dentato-rubral-pallido-luysian atrophy (DRPLA or a Haw River syndrome) in 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 (Table 1).

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

Table 1 Molecular characteristics of polyglutamine SCAs.

Features of mutagenesis in polyglutamine SCAs 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 – CAG sequence, which initially is repeated only several time (Dunnen, 2017). CAG sequence expansion usually takes place during mitosis of somatic and germ cells. Trinucleotide repeats expansion occurs by replication dependent (Kovtun et al., 2001), and reparation dependent (Kovtun et al., 2007) mechanisms. These disturbances are the cause of a phenomenon called “anticipation” – when the disease occurs progressively earlier and is more severe in subsequent generations. It was discovered that, the longer is the allele, the more it becomes unstable. The average number of CAG repeats expanded during reproduction depends on SCAs type (from +0.5 CAG repeats in SCA3 till +12 CAG repeats in SCA7) (Stevanin et al., 2000). Paternal alleles are more unstable during transmission which is probably due to a greater amount of mitotic divisions during sperm cell maturation compared to oocytes during

gametogenesis. However, it could also be linked with decreases in repair DNA proteins concentration and activity (Pearson et al., 2005).

The incidence of polyglutamine SCAs:

Total morbidity of polyglutamine SCAs is dramatically variable and varies around 1-9 per 100.000 with the more accurate accounts being 4-5 per 100.000.

SCA1 is observed, approximately, at the frequency of 1-2 people per 100.000 of “general” population (Manto et al., 2005). SCA2 has been revealed in 14% of cases of all SCAs, which makes about 0.6 per 100.000 population (Cancel et al., 1997; Geschwind et al., 1997b; Riess et al., 1997). SCA3 at some areas is the most common autosomal dominant SCA (Schols et al. 2004; Bauer et al. 2005b). The frequency of SCA3 is ~ 1.5-2 persons per 100,000 population (van de Warrenburg et al., 2002). World-wide incidence of SCA6 comes near 0.02-0.31 per 100,000 population (Geschwind et al., 1997; Ikeuchi et al., 1997; Matsumura et al., 1997; Matsuyama et al., 1997; Riess et al., 1997; Stevanin et al., 1997; Schols et al., 1998; Pujana et al., 1999; Jiang et al., 2005). The incidence of SCA7 in several studies was 2% of all SCA, 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 present time (~0,0015 per 100,000) (Maruyama et al., 2002; Alendar et al., 2004; Craig et al., 2005) (Figure 1A).

Figure 1

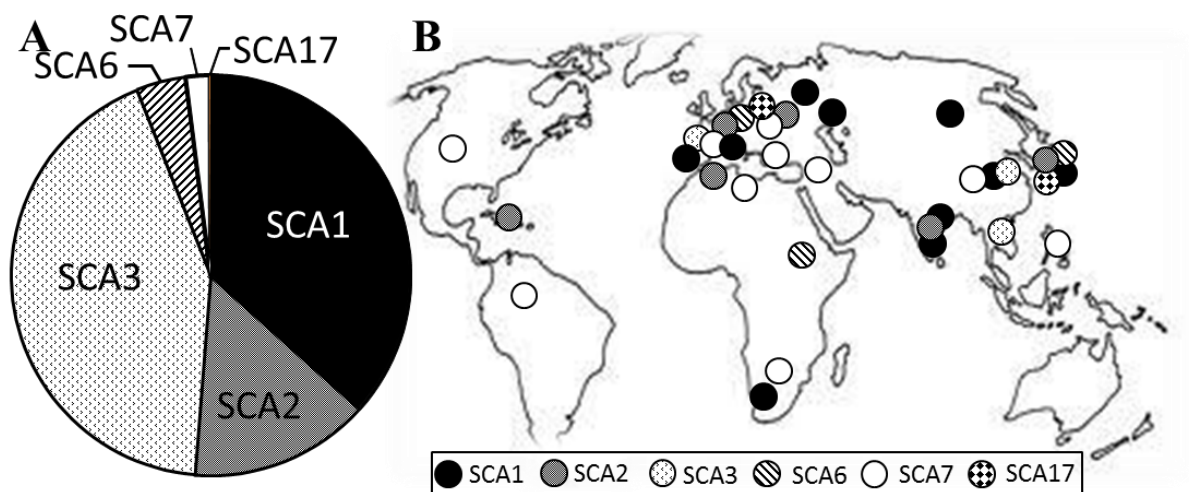


Figure legends:

Figure 1. Worldwide distribution of polyglutamine diseases. A. A 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).

Overall, about 60% of all clinical SCAs are the polyglutamine SCAs, whereas the other identified and accurately diagnosed forms comprise less than 5%. It is therefore important to note that 35-40% of SCAs have no established genetic base and are only characterized by the phenotype (Bird, 1998; Jayadev, 2013). At the same time, among polyglutamine SCAs, SCA1 and SCA3 comprise 2/3 of all registered cases (37% and 42% respectively) (Figure 1A).

Polyglutamine SCAs prevalence rate in Russia:

Research into polyglutamine diseases in Russia has been carried out for over 20 years. The incidence of polyglutamine SCAs in Russia is similar to those in the European populations, but there are also differences. From 105 Russian families (excluding the Yakut population) with polyglutamine diseases, SCA1, 2, 3, 6, 7 and 17 was diagnosed in 61 families. The incidence of SCAs are: SCA1 – 28 families (46%), SCA2 – 21 (34,4%), SCA3 - 7 (11,5%), SCA6 – 1 family and SCA7 – also 1 family (per 1,6%). SCA17 was founded in 3 families (Klyushnikov et al., 2016; Klyushnikov et al., 2017). Thus, characteristic in the Russian population is the low incidence of SCA3 whereas in populations of the USA and Japan it is the most frequent pathology (Klyushnikov et al., 2008). Notably, the incidence of SCA17 is very high in comparison to the distribution in global population.

It is interesting that preponderance of SCA1 over SCA3 is common in yet another population of Eastern Europe region, Poland. The morbidity of polyglutamine SCAs in Polish population is: SCA1 – 83,6%, SCA2 – 13,9%, SCA3 0,6%, SCA17 – 1,8% (Krysa et al., 2016).

Genetic aspects of origin and expansion of polyglutamine SCAs genesis:

Development of population genetics and paleogenetics, has allowed trace when polyglutamine SCAs have appeared in the human population. The mutation of a gene is quite unusual phenomenon, therefore such diseases are characterized by 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 allow to reveal the dynamics, common factors which affect the disease and predict the development of this pathology into 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) (Fig. 1B and Table 2). Usually, the speed of a mutation is higher and/or the mutation is older when it can be detected in wider populations or when it can be detected with higher incidence (Lund et al., 2000; Bettencourt, Lima, 2011). However, due to “anticipation” phenomenon, these two factors

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

Mutation rate	SCA	Haplotype	Place of inhabitation	References
Slow (time of origin 80000 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 and Shatunov 2004, Zhou et al., 2001
		Hindustan	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	Popova et al., 2001
		Polish	Wielkopolska and Lodz Voivodeship	Krysa et al., 2016
	SCA2	Western european	Germany, France	Didierjean et al., 1999
		Pan-european	France, Germany, Serbia	Didierjean et al., 1999
		North African	Morocco, Libya	Didierjean et al., 1999
		Caribbean	Jamaica, Cuba	Didierjean et al., 1999
		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	Stevanin et al., 1999
		Asiatic	Korea and Philippines	Stevanin et al., 1999
		Middle Eastern	Israel	
		Anglo-Saxon	UK, USA	Stevanin et al., 1999
		North African	Algeria, Morocco, Tunisia	Stevanin et al., 1999
		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

According to the mutation speed, age of clinical presentation and time of origin, polyglutamine SCAs can be divided conditionally into 2 groups. The first comprises diseases

with early presentation and low speed of a mutation – SCA3 and SCA6. 2-3 haplotypes are known for each polyglutamine disease.

In 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 characterized 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 (nearly 80000 years ago) (Craig et al., 2008). Asiatic haplotype of SCA3 arose in prehistoric period (nearly 7000 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 till the era of Great Geographical Discoveries. (Bettencourt, Lima, 2011). The active exploration by the Portuguese of the World Ocean, 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, however, there are also “younger” local haplotypes all over the World (Jayadev et al., 2006; Dichgans et al., 1999; Mori et al., 2001).

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 high level of mutations. The mutations that cause these diseases are relatively young - in most cases, they are present in only 1-20 generations and they 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 population of islands and remote areas with low migration rates (Wadia et al., 1998; Sinha et al., 2004; Mittal et al., 2005; Rengaraj et al., 2005; Wakisaka et al., 1995). In other regions such as Eastern Europe, migration was always high and it lead to spread of SCA1 to different parts of Eurasian continent. Prevalence of SCA1 in Russian population is due to presence of 3 specific haplotypes (Eastern European, Yakut and Bashkir) (Gouriev, 2004; Popova et al., 2001).

The same tendency could be seen in other polyglutamine SCAs with fast mutation rate (SCA2, SCA7 and SCA17). Here there is a big number of “young” haplotypes all over the World (Didierjean et al., 1999; Didierjean et al., 1999; Didierjean et al., 1999; Didierjean et al., 1999; Choudhry et al., 2001; Mizushima et al., 1998; Stevanin et al., 1999; Jonasson et al., 2000; Greenberg et al., 2006; Koide et al., 1999; Zühlke et al., 2005; De Michele et al., 2003; Zühlke et al., 2003). 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 the Africa, North and South parts are relatively well studied, and several haplotypes were found among the peoples living in these territories (Greenberg et al., 2006; Ramesar et al., 1997; Stevanin et al., 1999), whereas the Central 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 2 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 low migration history due to the remoteness of the place or ethnic characteristics, but also it could be linked to the 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 migration rate is the lowest in Japan (Statistics Japan, 1999; 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, the 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 the small populations in India, who obey a cast system, also leads to impressive consequences. Thus, SCA1, which is uncharacteristic for India, is observed in Tamil families living exclusively in the

two villages of Rajapalayam and Kottamedu of Tamil Nadu state, with a 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 the available data from the 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 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 from 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 rate (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 in the future to cover a wide range of populations in Africa, Asia and South America, which might change our understanding of not only 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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