

## MATERIALS OF THE REGULAR ISSUE

### ORIGINAL RESEARCHES

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## SPINOCEREBELLAR ATAXIA TYPE 1 AND PERSPECTIVE OF THERAPY

### ABSTRACT

Yakutia is an adverse region in the epidemiology of the autosomal dominant form of spinocerebellar ataxia type 1 (SCA1). Over the past 21 years, the number of carriers of the SCA1 mutation in the Republic Sakha (Yakutia) has reached 46 cases per 100,000 people of the Yakut population and is the highest in the world. Currently, there are no known effective methods of pathogenetic treatment. In general, symptomatic treatment of clinical manifestations of SCA1 is practiced. The article briefly describes the main results obtained to date in the world, on the disclosure of the molecular mechanism of the pathogenesis of SCA1 and ways to find promising means for the treatment of this disease.

**Keywords:** spinocerebellar ataxia type 1, pathogenesis, Purkinje cells, ataxin 1.

### Introduction

Yakutia is an adverse region in the epidemiology of the autosomal dominant form of spinocerebellar ataxia type 1 (SCA1). Over the past 21 years, the number of carriers of the SCA1 mutation in the Republic has reached 46 cases per 100,000 people and is the highest in the world [2]. Currently, there are no effective methods of pathogenetic treatment. In general, symptomatic treatment of clinical manifestations of SCA1 is practiced. The solution of medical and social problems of patients with SCA1 and the prevention of new cases is one of the urgent tasks of public health in the Republic Sakha. What are the prospects for treating this disease?

The mutation of SCA1 was identified 24 years ago by Huda Zoghbi (1993) in the laboratory of medicine and pathology of Professor Harry Orr in Medical School of the University of Minnesota. Currently, these researchers continue to study the molecular mechanisms of the pathogenesis and pathophysiology of the disease in order to search for innovative therapeutic developments. The scientific interests of these studies are related to the solution of the following issues: the molecular basis of the specificity of the pathology (atrophy of Purkinje cells), the mechanism of «distortion» of the function of the normal ataxin protein by the polyglutamine fragment, and the basis for the development of the risk of ataxia with increasing age of the organism. This article briefly describes the results of the main works and achievements of these authors in revealing the mechanism of the pathogenesis of SCA1 and the ways of finding promising means of treatment.

### Molecular mechanisms of the pathogenesis of SCA1

The study of the genetics of autosomal dominant SCA1 began in the mid-1970s when the gene associated with this pathology was first identified. As genetic technology developed, this gene was cloned (1993) and its structure studied [5]. Ataxin1 protein product is produced in many neurons of the brain, but Purkinje cells of the cerebellum are the most vulnerable to pathogenesis. This explains the clinical phenotype of the disease, selectivity of defeat and atrophy of Purkinje cells. Ataxin1-polypeptide composed of 816 amino acids. Studies have identified several structural elements of this polypeptide that are directly related to the function of protein in the body and its role in the pathogenesis of SCA1. First of all, an N-terminal sequence having a polyglutamine peptide fragment (up to 30 amino acids) with an insert inside the peptide of one or two amino acids of histidine. The mutant polypeptide does not have histidine inserts and is extended to 40-75 amino acids glutamine. The beginning of the debut of the disease depends on the length of the glutamine repeat. Genetic studies have shown that extended glutamine repeat in the gene of SCA1 enhances the function of this gene. This was proved on the model of a mutant mouse with loss of function of ataxin1 protein, where the clinical phenotype of SCA1 in mice does not develop. However, these mice show a memory deficit (skills acquired by Purkinje cells), which indicates the important functional significance of the organism's ataxin1 protein in the formation of memory of coordination of motor functions of the organism [4]. Thus, the pathogenesis of SCA1 is determined by the toxic effect of the

enhanced function of normal ataxin1 due to elongation of glutamine repeats. The studies revealed the main function of the gene in the body - the function of the transcription factor, in combination with other nuclear proteins it regulates the induction of gene expression responsible for the development of Purkinje cells. It was further shown that other structural elements of the polypeptide chain of this multifunctional protein have a modifying effect on the toxicity of this protein. These include the evolutionarily conserved AXH region (120 amino acid fragment) involved in the formation of a transcriptional complex with other proteins and regulation of gene expression. Another fragment of the polypeptide sequence determines the localization of ataxin binding in the nucleus of the Purkinje cell and the amino acid serine (776 position in the protein chain) phosphorylated by cellular kinase. Researchers also discovered the existence of adaptive dynamic changes in the morphology of Purkinje neurons for maintain the equilibrium of excitation functions (homeostasis) and the density of ion channels in the cell membrane. With excess excitation, parts of the dendritic branches of the neuron are removed (as temporary atrophy). This mechanism of maintaining equilibrium has its limits and the consequences of a change in the intensity of transcription, exceeding the equilibrium limit, lead to pathogenetic atrophy. This physiological feature of the neuron explains the late age onset of symptoms of SCA1. With age, the secondary process of atrophy is clinically manifested. This process allows to maintain vital for the physiology of Purkinje cells functions against the background of irreversible redundancy

and toxicity of transcription products of genes. This leads to an irreversible process of eliminating the branching of the neuron dendrites and further atrophy of the cell and tissue of the cerebellum. Thus, excessive expression with an «incorrect» function of ataxin 1 induces a number of toxic consequences for the Purkinje cell [3]. Studies on mouse models show an experimental possibility to weaken or eliminate toxicity of ataxin and the clinical phenotype of SCA1 by blocking the functioning of the above structural sections of ataxin protein 1. Investigations of the molecular mechanisms of the functioning of these sites open up new possibilities for finding promising directions from the point of view of therapy. The knowledge obtained in molecular genetic studies of this multifunctional protein is the basis for developing innovative approaches in the prevention and therapy of this disease. What are the ways, level and degree of development of these studies?

#### **Approaches for the search for promising ways to treat spinocerebellar ataxia**

Innovative developments are the result of using the knowledge of the molecular mechanism of the pathogenesis of the disease and are aimed at modifying the toxic effect of ataxin1 (attempts to change). These are the search for factors that inhibit gene expression at the level of transcription regulation, the process of chromatin decondensation, the translation of ataxin mRNA, as well as preventing the assembly of the protein molecule, its aggregation and toxic deposition.

The most promising approaches are: work with microRNAs to modulate protein synthesis, use chaperones to optimize assembly, protease inhibitors inducing apoptosis of neurons, work on the use of stem cells to repair brain tissue. Traditional searches of effective low-molecular chemical substances acting as cofactors of enzymes and stabilizers of multicomponent functional systems (derivatives of amino acids and carbohydrates) are also continuing to remove the severity of individual symptoms of the clinic of SCA1 [1]. Analysis of the mechanism of the pathogenesis of ataxia shows that the neurodegeneration of SCA1, carried out by ataxin 1 induces different pathological pathways. Therefore, effective treatment is possible with the combination of several therapeutic directions aimed at correcting different pathways of the disorder. In general, despite the great intellectual efforts of researchers, there seems to be a long way to find effective ways of pathogenetic treatment.

This work was supported by the Ministry of Education and Science of the Russian Federation (Project No. 17.6344.2017/8.9).

#### **REFERENCES**

1. Duenas A. M. Goold R., Giunti P. Molecular pathogenesis of spinocerebellar ataxias. *Brain* 2006: 1357-1370.
2. Platonov F.A., Tyryshkin K, Tikhonov DG, et.al. Genetic fitness and selection intensity in a population affected with high-incidence spinocerebellar ataxia type 1. *Neurogenetics* July 2016, Volume 17, Issue 3, pp 179–185. Doi: 10.1007/s10048-016-

0481-5.

3. Dell'Orco JM, Wasserman AH, Chopra R, et.al. Neuronal atrophy early in degenerative ataxia is a compensatory mechanism to regulate membrane excitability. *J. Neurosci* 2015: 12; 35 (32): 11292-11307.

4. Orr H.T. SCA1 – phosphorylation, a regulator of ataxin-1 function and pathogenesis. *Prog. Neurobiol* 2012: 99; 179-185.

5. Zoghbi HY. Orr H.T. Pathogenic mechanisms of a polyglutamine-mediated neurodegenerative disease. Spinocerebellar ataxia type 1. *JBC* 2009; 284: 7425-7429.

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