УДК 616.832.522-056.7-055.5/.7:577.21
https://doi.org/10.20538/1682-0363-2021-3-193-202

Genetics of familial amyotrophic lateral sclerosis

Savinova A.V.[1], Shnayder N. A.[1, 2], Nasyrova R.F.[1, 3]

[1] V.M. Bekhterev National Research Medical Center for Psychiatry and Neurology (V.M. Bekhterev NRMC PN)
3, Bekhterev Str., Saint Petersburg, 192019, Russian Federation

[2] V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (V.F. Voino-Yasenetsky KrasSMU)
1, Partizana Zheleznyaka Str., Krasnoyarsk, 660022, Russian Federation

[3] Kazan Federal University (KFU)
18, Kremlyovskaya Str., Kazan, 420008, Russian Federation

ABSTRACT

Aim. To analyze results of the studies covering modern scientific views on the genetics of familial amyotrophic lateral sclerosis (FALS).

Materials and methods. We searched for full-text publications containing the key words “amyotrophic lateral sclerosis”, “FALS”, and “genetics” in the literature for the past 10 years in both Russian and English in eLibrary, PubMed, Web of Science, and OMIM databases. In addition, the review includes earlier publications of historical interest.

This review summarizes all existing information on four most widespread genes associated with FALS: *SOD1*, *TARDBP*, *FUS,* and *C9ORF72*. The review also describes the functions of these genes and possible pathogenetic mechanisms of motor neuron death in amyotrophic lateral sclerosis (ALS), such as mitochondrial dysfunction, oxidative stress, glutamate excitotoxicity, damage to axonal transport components, and pathological neurofilament aggregation.

Conclusion. As modern methods of molecular genetic diagnostics evolve, our knowledge about multifactorial FALS genetics expands. This information should be taken into consideration in clinical practice of neurologists. Information about the genes associated with ALS and understanding of particular pathogenetic mechanisms of the disease play a key role in the development of effective therapeutic strategies.

Key words: amyotrophic lateral sclerosis, ALS, familial ALS, genetics, *SOD*, *FUS*, *TARDBP*, *C9ORF72.*

Conflict of interests. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Savinova A.V., Shnayder N.A., Nasyrova R.F. Genetics of familial amyotrophic lateral sclerosis. *Bulletin of Siberian Medicine.* 2021; 20 (3): 193–202. https://doi.org/10.20538/1682-0363-2021-3-193-202.

Генетика семейных форм бокового амиотрофического склероза

Савинова А.В.[1], Шнайдер Н.А.[1, 2], Насырова Р.Ф.[1, 3]

[1] Национальный медицинский исследовательский центр психиатрии и неврологии (НМИЦ ПН) имени В.М. Бехтерева
Россия, 192019, г. Санкт-Петербург, ул. Бехтерева, 3

✉ *Nasyrova Regina F.,* e-mail: nreginaf77@gmail.com

[2] *Красноярский государственный медицинский университет (КрасГМУ) имени профессора В.Ф. Войно-Ясенецкого*
Россия, 660022, г. Красноярск, ул. Партизана Железняка, 1

[3] *Казанский федеральный университет (КФУ)*
Россия,420008, г. Казань, ул. Кремлевская, 18

РЕЗЮМЕ

Анализируются результаты исследований, отражающих современное представление о генетике семейных форм бокового амиотрофического склероза (сБАС).

Проведен поиск полнотекстовых публикаций на русском и английском языках за последнее десятилетие в базах данных eLibrary, PubMed, Web of Science, OMIM, используя ключевые слова «боковой амиотрофический склероз» (БАС), «сБАС», «генетика». Кроме того, в обзор включены более ранние публикации, имеющие исторический интерес.

Представлены современные данные, накопленные по четырем самым распространенным генам возникновения сБАС: *SOD1*, *TARDBP*, *FUS* и *C9ORF72*. Рассмотрена функция этих генов, а также возможные патогенетические механизмы гибели мотонейронов при БАС: митохондриальная дисфункция, глутаматная эксайтотоксичноть, оксидативный стресс, поражение компонентов системы аксонального транспорта, патологическая агрегация нейрофиламентов.

По мере развития современных методов молекулярно-генетической диагностики расширяются знания в понимании генетики семейных мультифакторных форм БАС, что важно учитывать в клинической практике врачей-неврологов. Выявление генов, ответственных за возникновение БАС, а также понимание конкретных патогенетических механизмов развития заболевания играют ключевую роль в разработке эффективных терапевтических стратегий.

Ключевые слова: боковой амиотрофический склероз, БАС, семейный БАС, генетика, *SOD*, *FUS*, *TARDBP*, *C9ORF72*.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Савинова А.В., Шнайдер Н.А., Насырова Р.Ф. Генетика семейных форм бокового амиотрофического склероза. *Бюллетень сибирской медицины.* 2021; 20 (3): 193–202. https://doi.org/10.20538/1682-0363-2021-3-193-202.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by a loss of both central and peripheral motor neurons [1].

ALS occurs in 1.47–2.43 cases per 100 thousand people [2, 3]. The loss of neurons in ALS patients usually manifests itself in adulthood through such clinical symptoms as a loss of fine motor skills in limbs, intermittent claudication, and slurred speech. Over time, ALS symptoms progress and manifest themselves through limb paresis, muscular atrophy, fasciculations, and weight loss. In the end, this condition leads to death from respiratory failure within 32 months on average after the first manifestations.

ALS is considered to be a multifactorial disease. The exact etiology is currently unknown. However, scientists have described different pathogenetic mechanisms of motor neuron death in ALS: genetic factors [4, 5]; disruption in metabolism and ribonucleic acid (RNA) processing [6, 7]; glutamate excitotoxicity [8, 9]; oxidative stress [10]; mitochondrial dysfunction [11–13]; damaged axonal transport components [14, 15]; pathological neurofilament aggregation [16–18]; toxic effects of glial, dendritic, and antigen-presenting cells [19]. Even though ALS is mostly sporadic, 10% of cases are familial (heritable), which have both autosomal dominant (AD) and autosomal recessive (AR) inheritance patterns [20, 21].

Genetic etiology of ALS was first described in 1993 [22]. Further analysis of *SOD1* and neighboring

genes responsible for the development of the disease showed multiple pathogenic mutations that are specific for familial ALS (FALS) cases. Further connection analysis and sequencing of the ALS candidate genes led to the identification of genes associated with AD, AR, and X-linked inheritance of the disease [23]. Next generation sequencing expanded researchers' capabilities and significantly increased the identification of genes associated with ALS.

To date, more than 25 ALS loci and 4 loci of ALS combined with frontotemporal dementia (FTD) have been identified [24]. In most loci, specific genes causing the disease have been identified (Table).

Table

Genetic heterogeneity of ALS

Locus	Associated genes	Chromosomal location	Inheritance	OMIM
ALS 1	*SOD1*	21q22.11	AD (AR)	105400
ALS 2	*ALS2*	2q33.1	AR	
ALS 3	Unknown	18q21	AD	606640
ALS 4	*SETX*	9q34.13	AD	602433
ALS 5	*SPG11*	15q21.1	AR	602099
ALS 6	*FUS*	16p11.2	AD (AR)	608030
ALS 7	Unknown	20p13	AD	608031
ALS 8	*VAPB*	20q13.32	AD	608627
ALS 9	*ANG*	14q11.2	AD	611895
ALS 10	*TARDBP*	1p36.22	AD	612069
ALS 11	*FIG4*	6q21	AD	612577
ALS 12	*OPTN*	10p13	AD (AR)	602432
ALS 13	*ATXN2*	12q24.12	AD	183090
ALS 14	*VCP*	9p13.3	AD	613954
ALS 15	*UBQLN2*	Xp11.21	X-linked	300857
ALS 16	*SIGMAR1*	9p13.3	AD (AR)	614373
ALS 17	*CHMP2B*	3p11.2	AD	614696
ALS 18	*PFN1*	17p13.2	AD	614808
ALS 19	*ERBB4*	2q34	AD	615515
ALS 20	*hnRNPA1*	12q13.13	AD	615426
ALS 21	*MATR3*	5q31.2	AD	606070
ALS 22	*TUBA4A*	2q35	AD	616208
ALS 23	*ANXA11*	10q22.3	AD	617839
ALS 24	*NEK1*	4q33	AD	617892
ALS 25	KIF5A	12q13.3	AD	617921
ALS-FTD 1	*C9ORF72*	9p21.2	AD	105550
ALS-FTD 2	*CHCHD10*	22q11.23	AD	615911
ALS-FTD 3	*SQSTM1*	5q35.3	AD	616437
ALS-FTD 4	*TBK1*	12q14.2	AD	616439

Note: ALS – amyotrophic lateral sclerosis; ALS-FTD – ALS combined with frontotemporal dementia; OMIM – Online Mendelian Inheritance in Man; AD – autosomal dominant; AR – autosomal recessive.

This review summarizes the data from the studies of the four most common monogenic ALS forms caused by mutations in the *SOD1*, *TARDBP*, *FUS*, and *C9ORF72 genes*. Functions, contribution to the pathogenesis of ALS, and significance of these mechanisms for the development of new approaches to therapy were described for each gene in detail.

LOCUS ALS 1 (THE *SOD1* GENE)

The *SOD1* gene is located on the chromosome 21q22.11. This gene encodes superoxide dismutase 1, which is the main cytoplasmic antioxidant enzyme that binds copper and zinc and forms an extremely stable homodimer. SOD1 dimers are found in cytosol and intermembrane space of mitochondria. They provide an important antioxidant defense mechanism by catalyzing the production of oxygen and hydrogen peroxide from superoxide compounds, which are produced in cellular respiration [25].

SOD1 mutation was first described by D.R. Rosen et al. in 1993 and was the first identified genetic cause of FALS [22]. Most *SOD1* mutations are characterized

by AD inheritance [26]. However, cases of AR inheritance were also described [27, 28]. The rate of *SOD1* mutations varies from 12 to 23.5% in FALS patients and from 5 to 10% in sporadic ALS cases [29, 30]. Currently, more than 100 mutations of the *SOD1* gene have been described. The majority of them are point mutations. These point mutations are spread throughout the gene and do not provide functional or structural clues to better understanding of the FALS genesis. The reason for it is that the phenotype, duration, and severity of the disease can vary significantly depending on the sites involved. D90A is the most common variant of a missense mutation worldwide. Patients with A4V, H43R, L84V, G85R N86S, and G93A variants demonstrate rapid progression of the disease and a shorter life expectancy, while patients with G93C, D90A, and H46R variants usually have a longer life expectancy [31]. These mutations are accompanied by destabilization of the mutant protein molecule, which can be a trigger for disease development [32, 33].

Initially, mutations in the *SOD1* gene were considered to be linked to a decrease in the enzyme activity. This led to the assumption that the pathogenesis of ALS is associated with a loss of dismutase enzyme activity [22, 34]. However, a later study by D.W. Cleveland et al. (1995) showed that superoxide dismutase 1 (SOD1) activity does not correlate with the severity of the disease. This indicates that a toxic mechanism of the enzyme activity increase may be involved in the ALS pathogenesis [35]. Conformational and functional changes in *SOD1* induced by mutations exert their toxic effects through a number of mechanisms. These include excitotoxicity, oxidative stress, mitochondrial dysfunction, and prion-like propagation of mutant SOD1 (mtSOD1) [36]. mtSOD1 increases the levels of oxidative compounds (hydroxyl peroxide radicals [37–39], peroxynitrite [40]), which are toxic to cells. Besides, excessive enzyme activity of mtSOD1 is associated with the release of free zinc ions [41]. In addition, mtSOD bind to other proteins [42], for example, heat shock proteins, and disrupt their apoptotic activity [43, 44]. In general, redox regulation [45], mediated by excessive formation of toxic SOD1 aggregates [46], changes.

As in other neurodegenerative diseases associated with protein aggregation, the question of whether mutant forms of the protein are responsible for toxicity is being discussed. K. Forsberg et al. (2019) discovered granular SOD1-immunoreactive inclusions in motor neurons of FALS patients without pathogenic mutations in the *SOD1* gene. This may indicate that wrong conformation of SOD1 may be a consequence of a pathogenetic cascade associated with mutations in other genes (*C9ORF72HRE, FUS, KIF5A, NEK1, VAPB,* and *ALSIN*). Therefore, the authors suggest that new anti-SOD1 antibodies may be a promising therapeutic strategy in FALS [47].

LOCUS ALS 6 (GENE *FUS*)

The *FUS* gene is located on the chromosome 16p11.2. It was first identified as an oncogene in liposarcoma. The *FUS* gene encodes the ubiquitous 526 amino acid protein belonging to the FET family of RNA-binding proteins. Under normal physiological conditions, the FUS protein is localized mainly in the nucleus, but it can also pass into the cytoplasm while participating in nucleocytoplasmic transport [48]. FUS shares many physiological roles with TDP-43 (encoded by the *TARDBP* gene) such as transcription, pre-mRNA splicing, RNA transport, and translation regulation [49]. Even though they have much in common, TDP-43 and FUS regulate different processes associated with RNA [50, 51].

Currently, more than 50 different mutations in the *FUS* gene have been identified in FALS patients, and they are mainly characterized by AD inheritance. While most of these mutations are missense mutations, there are also rare cases of deletions, insertions, and nonsense mutations [52]. These mutations eventually lead to redistribution of FUS into the cytoplasm [53]. Other pathogenic variants of FUS increase the propensity of the protein to form aggregates. This reveals different pathomechanisms of the FALS genesis [54].

Y. Kino et al. (2015) proposed that FALS occurs following a decrease in the FUS protein function. Pathological redistribution of FUS into the cytoplasm makes it incapable of performing its functions in the nucleus [55].

In contrast to the theory of insufficient functional activity of FUS, scientists have put forward theories of the FALS genesis associated with an excessive toxic increase in the protein function. J.C. Mitchell et al. (2013) created a line of transgenic mice with excessive expression of FUS. As a result, this line of mice developed an aggressive ALS phenotype, in which the accumulation of cytoplasmic FUS was detected [56].

The question of whether neurotoxicity is a consequence of primary accumulation of FUS aggregates or a secondary increase in FUS in the cytoplasm after its redistribution is not fully explored. There is some evidence that toxicity can be caused directly by FUS aggregates. The accumulation of cytoplasmic FUS and

an aggressive phenotype were observed in the transgenic mouse models that express aggregate-prone FUS variants which lack the ability to recognize and bind RNA [57, 58]. There is also evidence that soluble cytoplasmic FUS may be toxic. Some studies on animal models of FALS (on transgenic rats in particular) demonstrated an increase in cytoplasmic FUS without aggregate formation [59–61]. S. Hennig et al. (2015) proposed that FUS aggregation can be a compensatory mechanism that protects cells from a toxic increase in soluble cytoplasmic FUS. The authors believe that the tendency of FUS to aggregate is not a pathological, but a normal cell function [62]. Impaired cellular function can also be a direct consequence of exposure to pathogenic FUS variants, which cause splicing defects, DNA damage, and disruption of FUS autoregulation [63, 64].

LOCUS ALS 10 (GENE *TARDBP*)

The *TARDBP* gene is located on the chromosome 1p36.22. It encodes TDP-43, a 414 amino acid DNA/RNA-binding protein. TDP-43 is usually localized in the nucleus, but it has both a nuclear localization signal and a nuclear export signal. This gives TDP-43 the ability to move freely between the nucleus and the cytoplasm [65]. TDP-43 regulates gene expression and participates in several stages of RNA processing: pre-mRNA splicing, regulation of mRNA stability, mRNA transport, translation, and regulation of non-coding RNA regions [66, 67].

Histological studies of the spinal cord specimens showed that neuronal ubiquitinated cytoplasmic inclusions were present in the majority of ALS patients [68]. However, in 2006, there was a change in the understanding of the FALS pathogenesis, when TDP-43 was discovered to be the main component of ubiquitinated protein aggregates found in FALS patients [69, 70]. Further histological studies confirmed that TDP-43 is present in cytoplasmic aggregates in most ALS patients, including sporadic cases without pathogenic variants in the *TARDBP* gene and in patients with hexanucleotide repeat expansions in *C9ORF72* [71, 72]. TDP-43 aggregation in ubiquitin-positive cytoplasmic inclusions of neurons in the brain and spinal cord is currently considered a distinctive pathological feature of ALS.

To date, at least 48 different *TARDBP* gene mutations have been associated with ALS development [53]. Most of these mutations are missense mutations located in the glycine-rich region at the carboxyl terminus of the transcript. The carboxy-terminal region interacts with other heterogeneous ribonucleoproteins and participates in the regulation of pre-mRNA splicing [73].

The cytoplasmic accumulation of TDP-43 is accompanied by redistribution of TDP-43 and its decrease in the nucleus. Due to this feature, a loss of normal TDP-43 function in the nucleus and / or a toxic increase in the protein function are proposed to be ALS development mechanisms.

Various animal models were created to test the hypothesis on function loss. In the absence of TDP-43, mice are not viable, which demonstrates that TDP-43 is vital for embryonic development [74]. Induced *TDP-43* knockout in adult mice is also lethal [75]. The mice that were heterozygous for *TARDBP* deletion showed motor deficits, but no degeneration of motor neurons and no decrease in the level of the TDP-43 protein were observed [74].

Most of the evidence for the increased function hypothesis comes from overexpression models. A neurodegeneration model was reproduced in the line of rodents with overexpression of TDP-43 of both wild and mutant types [76–78].

Both lack and overexpression of TDP-43 cause the disease. This emphasizes the importance of strictly controlled regulation of this protein. A. Koyama et al. (2016) discovered that a decrease in TDP-43 in the nucleus disrupts autoregulation and activates continuous synthesis of TDP-43 [79]. TDP-43 homeostasis is crucial for normal cellular function. An excess of TDP-43 in the cytoplasm can lead to formation of inclusions and cellular dysfunction, while nuclear depletion can cause dysregulation of mRNA metabolism [80, 81].

In addition to abnormal distribution and aggregation of TDP-43 in ALS, there is evidence of post-translational modifications associated with abnormal TDP-43. These modifications include ubiquitination, proteolytic cleavage, and phosphorylation [82]. The timing of these post-translational modifications and the role that each of them plays in the onset of the disease remain unclear.

LOCUS ALS-FTD 1 (GENE *C9ORF72*)

The *C9ORF72* gene is located on the chromosome 9p21.2. M. DeJesus-Hernandez et al. (2011) discovered that expansion of GGGGCC (G4C2) hexanucleotide repeats in the non-coding regions of the *C9ORF72* gene is one of the most common causes of ALS and FTD [6]. It is these expansions of hexanucleotide repeats that were found in 34% of FALS cases and 5% of sporadic ALS cases [4]. It is worth

mentioning that G4C2 repeats are more common in European populations than in Asian ones. Despite the fact that healthy people also have G4C2 hexanucleotide repeats, their number does not exceed 20, while in FALS patients, their number reaches hundreds and thousands [6].

Although the role of the *C9ORF72* gene in FALS development has already been established, the cellular function of the protein encoded by this gene has not yet been fully understood. Recent studies indicate that this gene participates in the regulation of vesicular transport [83]. C9ORF72 proteins co-localized with Rab proteins take part in autophagy and endocytosis. A.J. Waite et al. (2014) found out that in patients with ALS and hexanucleotide repeat expansion, the levels of the C9ORF72 protein and mRNA are decreased [84]. However, a loss of function in this gene alone cannot cause ALS symptoms independently [85].

Disruption of RNA processing plays a key role in the ALS development. Expansions of G4C2 repeats in the *C9ORF72* gene are located in the intron between the first two exons. Processing of such transcripts creates isoforms that contain one or both exons as well as a fragment of the expansion of G4C2 repeats [86].

Other possible processing disruptions include abortive transcription, impaired splicing of the intron containing G4C2 repeats, and nuclear aggregation [87]. Some of the transcripts that contain G4C2 repeats undergo RAN translation. This leads to the formation of pathological dipeptides that form inclusions in the central nervous system (CNS). It can also contribute to neurodegeneration [88]. Nuclear structures that disable RNA-binding proteins can be formed from RNA transcripts containing G4C2 repeats. These structures also affect RNA expression and splicing [89].

P. Fratta et al. (2012) point out that guanine-rich repeats are prone to formation of such a secondary DNA structure as a G-quadruplex. This promotes formation of pathological bonds with various proteins, which also inhibits transcription [90].

It is currently unknown which of the above-described mechanisms has the greatest influence on the ALS progression.

CONCLUSION

The studies analyzed above show a significant contribution of the mutations in the genes in question to the FALS pathogenesis. Further studies of the molecular genetic mechanisms behind the formation of these mutations will expand the understanding of the genetic mechanisms in the development of familial and multifactorial forms of ALS. This is important for further development of diagnostic approaches and pathogenetic therapeutic strategies in real clinical practice.

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Authors information

Savinova Alina V., Neurologist, Clinical Resident, V.M. Bekhterev NRMC PN, Saint Petersburg, Russian Federation. ORCID 0000-0002-7036-5326.

Shnayder Natalia A., Dr. Sci. (Med.), Professor, Leading Researcher, Department of Personalized Psychiatry and Neurology, V.M. Bekhterev NRMC PN, Saint Petersburg; Neurologist, Neurological Center of Epileptology, Neurogenetics, and Brain Research, University Clinic, V.F. Voino-Yasenetsky KrasSMU, Krasnoyarsk, Russian Federation. ORCID 0000-0002-2840-837X.

Nasyrova Regina F., Dr. Sci. (Med.), Principal Researcher, Head of the Department of Personalized Psychiatry and Neurology, V.M. Bekhterev NRMC PN, Saint Petersburg; Principal Researcher, Research Laboratory OpenLab "Gene and Cell Technologies", Institute of Fundamental Medicine and Biology (IFMB), KFU, Kazan, Russian Federation. ORCID 0000-0003-1874-9434.

(✉) **Nasyrova Regina F.,** e-mail: nreginaf77@gmail.com

Received 03.03.2020
Accepted 29.09.2020