Young-Onset Amyotrophic Lateral Sclerosis: Genetic Structure and Phenotypic Features

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Abstract

Introduction. *Young-onset amyotrophic lateral sclerosis (yALS) is a rare neurodegenerative disease characterized by the onset of clinical manifestations before the age of 45. The global prevalence, incidence, and genetic structure of yALS remain largely unknown, and the diagnosis is based primarily on clinical presentation, neurophysiologic findings, and molecular genetic analysis.*

Aim. *The aim of this study was to analyze cases of yALS in the Russian Center of Neurology and Neurosciences.*

Materials and methods. *A total of 365 ALS cases were analyzed, of which 47 (12.8%) patients met the criteria for yALS based on the age of onset and were included in this study. All patients underwent the necessary diagnostic procedures to exclude or establish a diagnosis. The coding sequence of the SOD1 gene was analyzed, and the size of the tandem hexanucleotide repeats $(GGGGCC)_n$ in the C9orf72 gene was evaluated. In some cases, massive parallel sequencing was performed.*

Results. *Mutations in causative ALS genes were detected in 15 (32%) patients: in 15% of cases, variants were found in the coding sequence of the SOD1 gene and 3' untranslated region, and in 8.7%, hexanucleotide repeat expansions $(GGGGCC)_n$ were found in the C9orf72 gene. In addition, in 4 (8.5%) yALS cases, mutations in the FUS, UBQLN2, and FIG4 genes were identified using massive parallel sequencing.*

Conclusion. *Early identification of both sporadic and familial forms of yALS and determination of their molecular genetic patterns is critical for timely genetic counseling and identification of potentially treatable etiologies.*

Keywords: *young-onset amyotrophic lateral sclerosis; juvenile amyotrophic lateral sclerosis; SOD1; UBQLN2; FUS*

Ethics approval. Written informed consent was obtained from patients for participation in the study and for the processing and presentation of the data obtained. The study was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 2-5/23 dated 15 February 2023).

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Боковой амиотрофический склероз с ранним началом: генетическая структура и фенотипические особенности

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Аннотация

Введение. *Боковой амиотрофический склероз с ранним началом (рнБАС) представляет собой редкое нейродегенеративное заболевание, характеризующееся началом клинических проявлений до 45-летнего возраста. Глобальная распространённость, заболеваемость и генетическая структура рнБАС остаются в значительной степени неизвестными, а диагноз основывается преимущественно на клинической картине, нейрофизиологических исследованиях и молекулярно-генетическом анализе.*

Целью *данного исследования является анализ случаев рнБАС, наблюдавшихся в Российском центре неврологии и нейронаук.*

Материалы и методы. *Проанализировано 365 случаев БАС, по возрасту дебюта критериям рнБАС удовлетворяли 47 (12,8%) пациентов, которые были включены в настоящее исследование. Всем пациентам проводили необходимый объём диагностических вмешательств для исключения/установления диагноза, анализировали кодирующую последовательность гена SOD1 и исследовали размер области тандемных гексануклеотидных повторов $(GGGGCC)_n$ в гене C9orf72, в отдельных случаях проводили массовое параллельное секвенирование.*

Результаты. *У 15 (32%) пациентов обнаружены мутации в каузальных генах БАС: в 15% случаев – варианты в кодирующей последовательности гена SOD1 и 3'UTR-области, в 8,7% – экспансия гексануклеотидных повторов $(GGGGCC)_n$ в гене C9orf72; в 4 (8,5%) случаях рнБАС методом массового параллельного секвенирования выявлены мутации в генах FUS, UBQLN2 и FIG4.*

Заключение. *Ранняя идентификация как спорадических, так и семейных форм рнБАС и установление их молекулярно-генетических основ имеют решающее значение для своевременного генетического консультирования и выявления потенциально поддающихся терапии этиологий.*

Ключевые слова: *боковой амиотрофический склероз с ранним началом; ювенильный БАС; SOD1; UBQLN2; FUS*

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Introduction

Amyotrophic lateral sclerosis (ALS) is the main form of both sporadic and hereditary neurodegenerative diseases in adults, collectively known as "motor neuron disease" [1]. ALS is more common in men, with a sex ratio in most populations ranging from 1.2 : 1.0 to 1.7 : 1.0 [2]. Most cases are classified as sporadic ALS, while 10% of patients have a family history of the disease, with two-thirds of them having mutations in ALS-associated genes [3]. Although ALS most commonly manifests between the ages of 50 and 70, in 10% of cases, the disease begins at a younger age, with symptoms appearing before the age of 45, and is classified as "young-onset ALS" (yALS) [4]. This subgroup of the disease is rare, and consequently, studies focusing on this age group are extremely limited [5, 6]. However, yALS is considered a variant of "classic" ALS with combined upper and lower motor neuron involvement and is typically represented by sporadic cases. yALS is characterized by several clinical features, including a less common bulbar onset, a predominance of upper motor neuron involvement, and a longer survival [7, 8]. Clinical cohort studies show that the young-onset phenotype is an independent prognostic factor for longer survival [7].

An extremely rare subgroup, usually included in the cohort of patients with yALS, consists of cases of juvenile ALS (jALS), which is defined as a form with the clinical onset before the age of 25 [7]. The global prevalence and incidence of jALS remain largely unknown. In one of the few multicenter studies, conducted in Europe and evaluating data from 46 specialized ALS centers, the annual prevalence of jALS was estimated to be 0.008 cases per 100,000 population for symptom onset before the age of 18, which accounts for less than 0.1% of all ALS cases [9]. In a Portuguese cohort of patients with yALS, jALS accounted for 14.3% of cases [6]. Since the clinical implementation of massive parallel sequencing, knowledge of the pathophysiological mechanisms of jALS has increased significantly, and the natural history and clinical manifestations of the different monogenic forms of jALS are better understood.

There are several important differences between jALS and adult-onset ALS. First, jALS has a greater genetic contribution: approximately 40% of cases are caused by specific mutations in ALS-specific genes [10, 11] compared to approximately 10% in adult-onset ALS [11]. Mutations in *FUS*, *SETX*, and *ALS2* genes are most commonly associated with jALS. Associations with mutations in *SPG11*, *SOD1*, *SPTLC1*, *UBQNL2*, *SIGMAR1* and other genes have also been reported. Mutations in the *C9orf72* gene, which are the most common in adult-onset ALS, have not been reported in jALS. Second, jALS is characterized by a polysyndromic pattern. In addition to the upper and lower motor neurons, other parts of the central or peripheral nervous system are involved in the pathological process.

In yALS and jALS, the pathological process may involve various neuronal pathways and, less commonly, brain regions responsible for cognition and emotion, and rarely sensory cortical areas. Some genetic subtypes associated with various dysfunctions of neurons and glial cells have been identified [6]. The loss of motor neurons in yALS and jALS is due to multiple pathophysiological mechanisms similar to those in typical forms of sporadic and familial ALS [1]. There is considerable pathophysiological and genetic overlap between jALS and other hereditary neurological disorders, including hereditary spastic paraplegias, axonal forms of hereditary motor and sensory neuropathies, spinal muscular atrophies not associated with the 5q locus, autosomal recessive cerebellar ataxias, and hereditary neurometabolic diseases [12–14].

It is important to systematize the available data and update the current understanding of yALS in light of advances in diagnostic techniques and new therapeutic strategies based on antisense oligonucleotides and viral vectors in gene therapy. This study presents the most important clinical and genetic aspects of patients with yALS and potential directions for developing therapies to treat this severe disease.

The **aim** of this study was to analyze cases of yALS in the Russian Center of Neurology and Neurosciences.

Materials and methods

The study was conducted at Neurology department No. 6 and the Molecular genetic laboratory of Neurology department No. 5 of the Russian Center of Neurology and Neurosciences from 2022 to 2025. A total of 365 ALS cases were analyzed, of which 47 (12.8%) patients met the criteria for yALS based on the age of onset (i.e., before the age of 45) and were included in the study.

Each patient underwent the necessary set of diagnostic procedures to exclude or establish ALS according to the revised El Escorial [15] and Gold Coast 2019 [16] criteria. The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) [17] was used to diagnose cognitive disorders. In addition to the standard clinical, neurophysiological, and neuroimaging examinations, all patients underwent molecular genetic testing, including analysis of the coding sequence of the *SOD1* gene by direct capillary Sanger sequencing and amplified fragment length analysis of the tandem hexanucleotide repeat $(GGGGCC)_n$ in the *C9orf72* gene by polymerase chain reaction with an additional primer for the repeat region. In some cases, patients with yALS and jALS underwent massive parallel sequencing. The whole exome sequencing panel was obtained from patients at other clinics.

Identified pathogenic variants, probable pathogenic variants, and variants of uncertain clinical significance were validated by capillary sequencing on a Nanophore 05 genetic analyzer (NPF Syntol) in the Molecular genetics laboratory of Neurology department No. 5 of the Russian Center of Neurology and Neurosciences.

Written informed consent was obtained from patients for participation in the study and for the processing and presentation of the data obtained. The study was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 2-5/23 dated 15 February 2023).

Results

The study included 365 patients with confirmed ALS according to the current criteria. Of these, 47 (12.8%) patients met the age criteria for yALS, including 15 (32%) patients identified as carriers of mutations in ALS-associated genes (Table 1).

Seven (14.8%) *SOD1*gene mutations, including 6 in the coding region and one in the 3' untranslated region (3'UTR), were identified by coding sequence analysis. In addition, 5 (11%) cases were familial forms of *SOD1*-associated ALS, predominantly with an autosomal dominant inheritance, whereas the others were classified as sporadic (4%). The most common mutations in the *SOD1* gene, typical of yALS, included the *p.Asp91Ala* and *p.Asn140Asp* mutations previously described in other populations.

Based on the number of hexanucleotide repeats $(GGGGCC)_n$ in the *C9orf72* gene, an expansion was identified in 4 (8.5%) cases, with the number of repeats exceeding the threshold of 50 copies in all cases. Most studies define a pathological repeat threshold of > 35 [18, 19].

As for jALS, massive parallel sequencing was recommended for all 4 patients because this form of ALS is extremely rare. The results were obtained from the patients for genotype-phenotype correlation analysis and validation of the identified vari-

Table 1. Clinical and genetic profile of patients

No.	Age of onset / sex	Gene / locus	Exon / intron	Genetic variant	Amino acid substitution	Type of inheritance	Form of disease onset
1	38 / male	*c9orf72*/ 9p21.2	1	rs143561967	—	Sporadic	Cervicothoracic
2	36 / female	*c9orf72*/ 9p21.2	1	rs143561967	—	Autosomal dominant	Bulbar
3	44 / male	*c9orf72*/ 9p21.2	1	rs143561967	—	Sporadic	Cervicothoracic
4	33 / female	*c9orf72*/ 9p21.2	1	rs143561967	—	Sporadic	Bulbar
5	43 / male	*SOD1*/ 21q22.11	3'UTR	rs2516661924	—	Sporadic	Lumbosacral
6	35 / female	*SOD1*/ 21q22.11	5	rs1568811471	NP_000445.1: *p.Asn140Asp*	Autosomal dominant	Lumbosacral
7	37 / female	*SOD1*/ 21q22.11	5	rs1568811471	NP_000445.1: *p.Asn140Asp*	Autosomal dominant	Lumbosacral
8	41 / male	*SOD1*/ 21q22.11	4	rs80265967	NP_000445.1: *p.Asp91Ala*	Autosomal dominant	Lumbosacral
9	37 / female	*SOD1*/ 21q22.11	4	rs80265967	NP_000445.1: *p.Asp91Ala*	Sporadic	Lumbosacral
10	41 / female	*SOD1*/ 21q22.11	4	rs80265967	NP_000445.1: *p.Asp91Ala*	Autosomal dominant	Lumbosacral
11	37 / male	*FIG4*/ 6q21	5	rs1455052760	NP_055660.1: *p.Val157Met*	Autosomal dominant / incomplete penetrance	Cervicothoracic
12	24 / female	*SOD1*/ 21q22.11	5	*de novo*	NP_000445.1: *p.Glu134Gly*	Autosomal recessive	Lumbosacral
13	5 / male	*UBQLN2*/ Xp11.21	1	rs764837088	NP_038472.2: *p.Thr134Ile*	Sporadic	Associated with cognitive disorders
14	20 / male	*FUS*/ 16p11.2	14	rs387906627	NP_004951.1: *p.Arg495Ter*	Autosomal dominant	Bulbar
15	18 / male	*FUS*/ 16p11.2	14	rs387906627	NP_004951.1: *p.Arg495Ter*	Sporadic	Bulbar

ants. In 2 cases of jALS, a *p.Arg495Ter* mutation in the *FUS* gene was identified. In one case, the disease was hereditary, in the other it was sporadic with a *de novo* mutation not found in the proband's parents. Variants in the *SOD1* gene (*p.Glu134Gly*) for a familial form and *UBQLN2* (*p.Thr134Ile*) for a *de novo* mutation were also identified as the cause of the ASL.

In the structure of yALS phenotypes with identified mutations, the lumbosacral onset (47%) was predominant, which is typical for *SOD1*-associated cases. In 4 (27%) cases, a bulbar onset of symptoms was observed, which is typical of mutations in the *C9orf72* and *FUS* genes. In 3 (20%) patients, a cervicothoracic yASL was associated with mutations in the *C9orf72* and *FIG4* genes. An extremely rare jALS phenotype with a predominance of upper motor neuron involvement and multimodal cognitive impairment was associated with a mutation in the *UBQLN2* gene.

One patient with a confirmed yALS provided a result of whole exome sequencing that identified a heterozygous *p.Val157Met* mutation in the *FIG4* gene of uncertain clinical significance. Validation of the identified variant revealed that the *p.Val-157Met* mutation was heterozygous in the clinically healthy mother of the proband. A genetic structure of the identified mutations is presented in Figure 1.

Discussion

This study provides the only detailed description of the genetic structure and phenotypic features of a cohort of

patients with yALS in Russia. The predominant form of disease onset in patients with yALS was found to be spinal (67% of patients with identified mutations), affecting the lower limbs (lumbosacral form) and/or upper limbs (cervicothoracic form). Most cases showed a lumbosacral onset of symptoms. The bulbar form was found in 27% of patients with confirmed mutations in causative ALS genes. Large European population studies showed that the percentage of bulbar forms increases with the age of symptom onset, reaching 10–51% in men and 6–72% in women [20, 21]. A low incidence of bulba-onsetr forms in patients with onset before age 41 (mean: 16%) contrasts with a higher incidence in older patients (mean: 43% for onset after age 70) [7]. Our data are consistent with these studies and confirm a higher percentage of spinal-onset forms in the structure of yALS.

Four key causative genes are known to explain approximately 48% of familial ALS cases and approximately 5% of sporadic ALS cases in populations of European origin [11]. These genes are *C9orf72*, *SOD1*, *TARDBP*, and *FUS*. In this study, 15% of yALS cases were associated with mutations in the *SOD1* gene, and the most common mutations were *p.Asp91Ala* and *p.Asn140Asp* previously described in the European population. Lumbosacral ALS was the predominant clinical form. The data obtained are consistent with known studies [22], which report a higher percentage of spinal manifestations, especially with weakness in the lower limbs (lumbosacral form). However, a well-defined phenotype is only known for some mutations in the *SOD1* gene, such as the *D90A* mutation (one of the most common in Europe), which is characterized by a slow progression and lumbosacral onset.

The hexanucleotide $(GGGGCC)_n$ expansion in the non-coding region of the *C9orf72* gene is the most common cause of familial ALS [19]. According to studies conducted [23], the percentage of *C9orf72* mutations responsible for the development of ALS ranges from 7.84% to 41% in patients with a positive family history and is approximately 5% in sporadic cases, depending on the study population. Our study showed that mutations in the *C9orf72* gene were causative in 8.7% of cases, and only one patient had a significant family history, whereas in the other cases were sporadic. Bulbar ALS and cervicothoracic ALS were the most common forms associated with mutations in the *C9orf72* gene. Our data are consistent with one of the large cohort studies on the clinical and genetic features of *C9orf72*-associated ALS, which showed that the first symptoms often affect the bulbar level of the cerebrospinal axis, and the mean age of onset is 58 years, characterizing the hexanucleotide expansion in the *C9orf72* gene as an extremely rare cause of yALS [19].

In 2009, a rare autosomal dominant form of ALS associated with heterozygous pathogenic variants in the *FIG4* gene was first described in patients from North America [24]. *FIG4* encodes a phosphoinositide 5-phosphatase involved in the regulation of phosphatidylinositol-3,5-bisphosphate, which is an intracellular signaling lipid that plays a key role in the transport of endosomal vesicles. Loss of function leads to neurodegenerative processes in the central nervous system, including spinal cord motor neurons, as well as peripheral neuropathy, which has been demonstrated in animal models [25]. To date, at least 14 rare non-synonymous variants

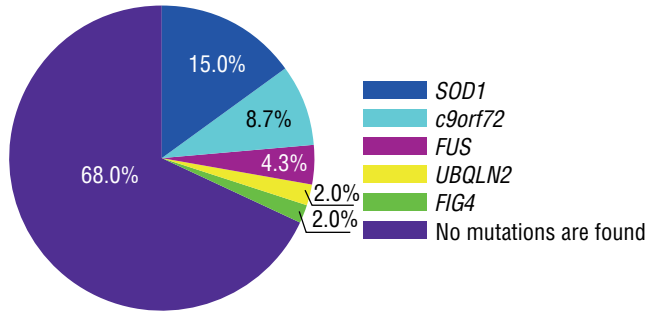

Fig. 1. Distribution of mutations in ALS causative genes in 47 patients with yALS observed at the Neurology Department No. 6 of the Russian Center of Neurology and Neurosciences.

in the *FIG4* gene have been identified, and the contribution of these variants to the pathogenesis of ALS remains controversial, because pathogenic *FIG4* variants were not detected in small patient cohorts, and some carriers of such variants showed incomplete penetrance (absence of clinical manifestations despite the presence of a mutation) [26, 27]. Incomplete penetrance probably explains the absence of clinical manifestations in the proband's mother, who was also a carrier of the heterozygous *p.Val157Met* mutation in the *FIG4* gene. The clinical phenotype in the proband was represented by signs of predominant upper motor neuron involvement, which is also a typical feature of *FIG4*-associated ALS [28], as well as by a cervicothoracic onset. The contribution of environmental factors as ALS risk modifiers is being investigated because even causative mutations may have incomplete penetrance. Potential exogenous factors associated with ALS include toxic factors (such as radiation, pesticides, organic solvents, β-methylamino-L-alanine, methylphenyl tetrahydropyridine, heavy metals, vaccination), infectious factors (such as retroviruses, herpesviruses), and environmental and lifestyle factors (such as dietary habits, low intake of polyunsaturated fatty acids, intense physical activity, sports, repeated traumatic brain injury, occupational exposure to electromagnetic fields, etc.) [1]. These factors can act as potential triggers for yALS in the presence of a genetic predisposition [1, 29].

The most common genetic basis associated with jALS includes mutations in the *FUS*, *ALS2*, *SETX*, and *SPG11* [29]. Autosomal recessive inheritance is more common in consanguineous families and has been described in patients with variants in *ALS2*, *SPG11*, *SIGMAR1*, *ERLIN1*, *VRK1*, *GNE*, *DDHD1*, and *SYNE1* genes. Autosomal dominant inheritance and sporadic cases with *de novo* mutations are more commonly associated with variants in the *FUS* [30], *SETX*, *SOD1*, *SPTLC1* [31], *SPTLC2*, *TRMT2B*, *BICD2*, and *TARDBP* genes. X-linked inheritance is typical of rare pathogenic variants in the *UBQLN2* gene [32], although it has been described in extremely rare cases for mutations in the *TRMT2B* gene [33]. Pathogenic variants in the *FUS* and *SOD1* genes represent the most common monogenic forms of familial jALS with a global prevalence, despite the fact that most cases of jALS are sporadic and are caused by *de novo* mutations [34].

The current literature shows that *SOD1* mutations are associated with three cases of jALS [35–37]. These cases are

characterized by disease onset in the late second or early third decade of life, accompanied by a combination of symptoms of both upper and lower motor neuron involvement. All patients progressed rapidly and developed respiratory failure. Two patients died less than two years after the onset of symptoms. These mutations were considered to be *de novo*, because no clear family history could be identified. Patients with *SOD1*-associated jALS had no signs of sensory or cognitive impairment. Electromyography showed active denervation and chronic neurogenic changes. Sensory conduction parameters remained normal. Neuropathologic examination revealed severe degeneration of the anterior horns of the spinal cord, Bunina bodies, and gliosis in the spinal cord and brain in one patient [37]. Ubiquitin-immunoreactive inclusions and the SOD1 protein were found in the neurons of the anterior horns. An important feature of *SOD1* mutations in jALS is that they are located near zinc-binding sites [35, 37] or in the β-structural domains of the protein [36] and in most cases differ from mutations detected in adult-onset ALS.

In our case of *SOD1*-associated jALS, the onset of symptoms was reported at the age of 24. The clinical presentation was characterized by predominant lower motor neuron involvement and a rapid progression of neurological deficit, leading to almost complete immobilization of the patient within 6 months of progression and death from severe respiratory failure 10 months after the onset of symptoms. The patient was a homozygous carrier of the *p.E134G* variant, whereas the proband's mother (a heterozygous carrier) showed no signs of the disease, which may indicate autosomal recessive inheritance. This clinical case is interesting because *SOD1* mutations most often have an autosomal dominant inheritance type and full penetrance [22], but some studies have shown that *SOD1*-associated ALS can also have a recessive inheritance type [38], and it is also known that incomplete penetrance of *SOD1* mutations is extremely rare [39]. This variant was previously described in one study [40] as a cause of sporadic ALS with a lumbosacral onset at the age of 34 and a slow progression rate.

UBQLN2 is a transport protein involved in the function of the ubiquitin-proteasome system. Disruption of the ubiquitin-proteasome system caused by UBQLN2 mutations is one of the most actively studied mechanisms of the pathogenesis associated with UBQLN2. However, the role of the UBQLN2 protein in disrupting the cytoplasm localization of TDP-43 protein and its aggregation into insoluble inclusions, which is typical of ALS, is well established. Recent studies show that *UBQLN2* mutations associated with ALS also lead to abnormal autophagy, neuroinflammation, and abnormal formation of stress granules [41]. Taken together, these data underscore the key role of UBQLN2 in the pathogenesis of ALS and frontotemporal dementia associated with abnormal metabolism of toxic proteins and failure of their clearance mechanisms.

In one study that included five families with rare cases of jALS, *UBQLN2* mutations were characterized by an X-linked dominant inheritance pattern and also manifested in disease forms combined with dementia [32]. The age of clinical manifestation in *UBQLN2*-associated ALS ranged from 16 years to 71 years. The mean age of onset was 33.9 ± 14.0 years in men and 47.3 ± 10.8 years in women. The mean duration of the disease was about four decades, indicating its slow progression. Frontotemporal dementia is most often associated with *UBQLN2* mutations. Of 40 patients with *UBQLN2* mutations, three had disease onset before the age of 24. One patient had the classic presentation of ALS, another patient had a combination of ALS and frontotemporal dementia, and the third patient had a combination of upper motor neuron signs and dementia. Spinal cord pathomorphology in two patients showed degeneration of anterior horn neurons, atrophy of corticospinal tracts, and severe astrocytosis.

Our case presented a pediatric onset of ALS at the age of 5–6 years with delayed psychomotor development, hand tremor (probably due to muscle weakness) and calf muscle spasms with gradual addition of leg weakness over 10 years. The rate of disease progression in this clinical case can certainly be considered slow, which is consistent with the literature data, and the prognosis can be considered favorable, also due to the absence of respiratory dysfunction. A characteristic feature of our case is the combination of multimodal cognitive impairment, lower motor neuron involvement, which is clinically manifested as mild tongue tremor and marginal hypotrophy, cramps and spontaneous fasciculations in the arms, legs and abdominal muscles, and neurophysiologically manifested as a long-term (for several years) slowly progressive, generalized peripheral motor neuron involvement with a strong predominance of the reinnervation process over denervation, and upper motor neuron involvement manifested as increased deep tendon and periosteal reflexes and mild spastic hypertonia in the legs.

The *FUS* gene is considered one of the most frequent causes of jALS [34]. However, *FUS*-associated cases show considerable phenotypic variability, ranging from classic adult onset to aggressive forms with onset in childhood. Both in juvenile and pediatric populations, the disease with mutations in the *FUS* gene is generally more malignant and rapidly progressive. The pediatric group shows an extremely limited number of genes associated with classic ALS, and this disease is rare and often underestimated in the differential diagnosis of motor neuron diseases in children. However, cases associated with *FUS* mutations are disproportionately represented in this age category.

The reasons why the same gene can cause both an aggressive, early (pediatric) form of ALS and a classic adult-onset form remain unclear. The *FUS* gene is located on chromosome 16 and encodes a protein involved in some important processes related to the regulation of DNA and RNA functions. The literature suggests that the variability of clinical phenotypes may be related to the location of mutations within different functional domains of the *FUS* gene.

Analysis of 38 published cases of *FUS*-associated jALS showed that most of them are caused by *de novo* mutations [42]. The *FUS* mutations associated with jALS differ from *FUS* mutations typical of later-onset ALS, although both are often located in the C-terminal fragment of the protein [43]. The age of disease onset is usually 21 years. The clinical presentation of *FUS*-associated jALS includes signs of both lower and upper motor neuron involvement such as muscle weakness,

hypotrophy combined with spasticity and hyperreflexia. *FUS*-associated jALS is characterized by rapid progression with a fatal outcome due to respiratory failure within 1–2 years from the onset of symptoms. Although bulbar onset is usually associated with faster progression, no significant differences in survival between spinal and bulbar forms of ALS have been identified in young age [43]. In some cases of *FUS*-associated ALS, movement disorders are described, such as myoclonic jerks [44], tremors, and in even rarer cases, oculomotor disorders manifested as diplopia [45].

In two of our cases, a previously described pathogenic *p.Arg495Ter* mutation in the *FUS* gene was found, which leads to the premature appearance of a stop codon, resulting in the truncation of the C-terminal fragment of the FUS protein. The literature shows that this nucleotide variant is associated with an aggressive disease phenotype [46], although the molecular mechanisms of such a malignant clinical presentation currently remain unclear. In the first clinical case, the identified mutation appeared to be inherited from the father, who developed signs of bulbar and respiratory dysfunction at the age of 29, progressing steadily to a fatal outcome at the age of 35. In another clinical case, the identified mutation was not inherited from the parents and, according to the trio analysis, it was a *de novo* variant, which is also consistent with the literature, because most published cases of *FUS*-associated jALS are *de novo* mutations [42].

The main phenotypic difference in our cases of *FUS*-associated jALS is that in the case of the hereditary disease, the onset of symptoms was represented by classic progressive bulbar palsy, which was later accompanied by facial muscle weakness and progressive neurogenic respiratory disorders, whereas in the sporadic *FUS*-associated jALS, the first symptom was facial asymmetry (facial diplegia) with later development of bulbar disorders.

The prognosis for ALS remains largely unpredictable. Although for most patients the course of the disease is similar to classical ALS, with a life expectancy from symptom onset to fatal outcome of 20–48 months [47], more than 10% of patients survive for more than 10 years [48]. Data on the natural history of the various genetic subtypes of jALS are extremely limited, and case series are the most valuable. In general, most young-onset and juvenile forms are characterized by a longer surviva;. However, even with relatively slow progression, patients experience a significant decrease in quality of life, significant loss of functional independence, and often require nutritional support, gastrostomy, and continuous respiratory support and mechanical ventilation [49]. Childhood onset, bulbar onset, and jALS with more complex neurological manifestations usually have a severe course and an unfavorable prognosis [29]. A rapid clinical progression is especially typical of jALS subtypes associated with *FUS* and *SOD1* mutations [29, 50].

Conclusions

Young-onset ALS is a rare neurodegenerative disease with many unmet diagnostic and therapeutic challenges. The diagnosis is based primarily on clinical manifestations, neurophysiological findings, and molecular genetic analysis. However, a definitive diagnosis is not necessarily based on a monogenic cause. Early identification of both sporadic and familial forms of yALS and determination of their molecular genetic patterns is critical for timely genetic counseling and identification of potentially treatable etiologies. Clinical trials are underway for some genetic causes associated with ALS. At the time of this publication, antisense oligonucleotide-based agents for the treatment of *SOD1*- and *FUS*-associated ALS are in phase III clinical trials and are showing promising results.

References | Список источников

1. van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. *Lancet*. 2017;390(10107):2084–2098. doi: 10.1016/S0140-6736(17)31287-4
2. Marin B, Logroscino G, Boumédiene F, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. *Eur J Epidemiol.* 2016;31(3):229–245. doi: 10.1007/S10654-015-0090-X
3. Chia R, Chiò A, Traynor BJ. Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. *Lancet Neurol.* 2018;17(1):94–102. doi: 10.1016/S1474-4422(17)30401-5
4. Deng J, Wu W, Xie Z, et al. Novel and recurrent mutations in a cohort of Chinese patients with young-onset amyotrophic lateral sclerosis. *Front Neurosci.* 2019;13:1289. doi: 10.3389/fnins.2019.01289
5. Lin J, Chen W, Huang P, et al. The distinct manifestation of young-onset amyotrophic lateral sclerosis in China. *Amyotroph Lateral Scler Frontotemporal Degener.* 2021;22(1-2):30–37. doi: 10.1080/21678421.2020.1797091
6. Oliveira Santos M, Gromicho M, Pinto S, et al. Clinical characteristics in young-adult ALS – results from a Portuguese cohort study. *Amyotroph Lateral Scler Frontotemporal Degener.* 2020;21(7-8):620–623. doi: 10.1080/21678421.2020.1790611
7. Turner MR, Barnwell J, Al-Chalabi A, et al. Young-onset amyotrophic lateral sclerosis: historical and other observations. *Brain.* 2012;135 (Pt 9):2883–2891. doi: 10.1093/BRAIN/AWS144
8. Sabatelli M, Madia F, Conte A, et al. Natural history of young-adult amyotrophic lateral sclerosis. *Neurology.* 2008;71(12):876–881. doi: 10.1212/01.WNL.0000312378.94737.45
9. Kliest T, Van Eijk RPA, Al-Chalabi A, et al. Clinical trials in pediatric ALS: a TRICALS feasibility study. *Amyotroph Lateral Scler Frontotemporal Degener.* 2022;23(7-8):481–488. doi: 10.1080/21678421.2021.2024856
10. Kacem I, Sghaier I, Bougatef S, et al. Epidemiological and clinical features of amyotrophic lateral sclerosis in a Tunisian cohort. *Amyotroph Lateral Scler Frontotemporal Degener.* 2020;21(1-2):131–139. doi: 10.1080/21678421.2019.1704012
11. Mathis S, Goizet C, Soulages A, et al. Genetics of amyotrophic lateral sclerosis: a review. *J Neurol Sci.* 2019;399:217–226. doi: 10.1016/JJNS.2019.02.030
12. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, et al. Hereditary spastic paraplegia: clinical and genetic hallmarks. *Cerebellum.* 2017;16(2):525–551. doi: 10.1007/S12311-016-0803-Z
13. Connolly O, Le Gall L, McCluskey G, et al. A systematic review of genotype-phenotype correlation across cohorts having causal mutations of different genes in ALS. *J Pers Med.* 2020;10(3):58. doi: 10.3390/JPM10030058
14. Souza PVS, Pinto WBVR, Ricarte A, et al. Clinical and radiological profile of patients with spinal muscular atrophy type 4. *Eur J Neurol.* 2021;28(2):609–619. doi: 10.1111/ENE.14587
15. Ludolph A, Drory V, Hardiman O, et al. A revision of the El Escorial criteria – 2015. *Amyotroph Lateral Scler Frontotemporal Degener.* 2015;16(5-6):291–292. doi: 10.3109/21678421.2015.1049183
16. Turner MR, Group UMCS. Diagnosing ALS: the Gold Coast criteria and the role of EMG. *Pract Neurol.* 2022;22(3):176–178. doi: 10.1136/PRACTNEUROL-2021-003256
17. Niven E, Newton J, Foley J, et al. Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): a cogni-

tive tool for motor disorders. *Amyotroph Lateral Scler Frontotemporal Degener*. 2015;16(3-4):172–179. doi: 10.3109/21678421.2015.1030430
18. Van Mossevelde S, van der Zee J, Cruts M, et al. Relationship between C9orf72 repeat size and clinical phenotype. *Curr Opin Genet Dev*. 2017;44:117–124. doi: 10.1016/J.GDE.2017.02.008
19. Wiesenfarth M, Gunther K, Muller K, et al. Clinical and genetic features of amyotrophic lateral sclerosis patients with C9orf72 mutations. *Brain Commun*. 2023;5(2):fcad087. doi: 10.1093/BRAINCOMMS/FCAD087
20. Beghi E, Millul A, Micheli A, et al. Incidence of ALS in Lombardy, Italy. *Neurology*. 2007;68(2):141–145. doi: 10.1212/01.WNL.0000250339.14392.BB
21. Chiò A, Calvo A, Moglia C, et al. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry*. 2011;82(7):740–746. doi: 10.1136/JNNP.2010.235952
22. Berdyński M, Miszta P, Safranow K, et al. SOD1 mutations associated with amyotrophic lateral sclerosis analysis of variant severity. *Sci Rep*. 2022;12(1):103. doi: 10.1038/S41598-021-03891-8
23. Umoh ME, Fournier C, Li Y, et al. Comparative analysis of C9orf72 and sporadic disease in an ALS clinic population. *Neurology*. 2016;87(10):1024–1030. doi: 10.1212/WNL.0000000000003067
24. Chow CY, Landers JE, Bergren SK, et al. Deleterious variants of FIG4, a phosphoinositide phosphatase, in patients with ALS. *Am J Hum Genet*. 2009;84(1):85–88. doi: 10.1016/J.AJHG.2008.12.010
25. Chow CY, Zhang Y, Dowling JJ, et al. Mutation of FIG4 causes neurodegeneration in the pale tremor mouse and patients with CMT4J. *Nature*. 2007;448(7149):68–72. doi: 10.1038/NATURE05876
26. Tsai CP, Soong BW, Lin KP, et al. FUS, TARDBP, and SOD1 mutations in a Taiwanese cohort with familial ALS. *Neurobiol Aging*. 2011;32(3):553.e13-21. doi: 10.1016/J.NEUROBIOLAGING.2010.04.009
27. Verdiani S, Origone P, Geroldi A, et al. The FIG4 gene does not play a major role in causing ALS in Italian patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14(3):228–229. doi: 10.3109/21678421.2012.760605
28. Yilihamu M, Liu X, Liu X, et al. Case report: a variant of the FIG4 gene with rapidly progressive amyotrophic lateral sclerosis. *Front Neurol*. 2022;13:984866. doi: 10.3389/FNEUR.2022.984866
29. Lehky T, Grunseich C. Juvenile amyotrophic lateral sclerosis: a review. *Genes (Basel)*. 2021;12(12):1935. doi: 10.3390/GENES12121935
30. Conte A, Lattante S, Zollino M, et al. P525L FUS mutation is consistently associated with a severe form of juvenile amyotrophic lateral sclerosis. *Neuromuscul Disord*. 2012;22(1):73–75. doi: 10.1016/J.NMD.2011.08.003
31. Johnson JO, Chia R, Miller DE, et al. Association of variants in the SPTLC1 gene with juvenile amyotrophic lateral sclerosis. *JAMA Neurol*. 2021;78(10):1236–1248. doi: 10.1001/JAMANEUROL.2021.2598
32. Deng HX, Chen W, Hong ST, et al. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. *Nature*. 2011;477(7363):211–215. doi: 10.1038/NATURE10353
33. Liu Y, He X, Yuan Y, et al. Association of TRMT2B gene variants with juvenile amyotrophic lateral sclerosis. *Front Med*. 2024;18(1):68–80. doi: 10.1007/S11684-023-1005-Y
34. Chen L. FUS mutation is probably the most common pathogenic gene for JALS, especially sporadic JALS. *Rev Neurol (Paris)*. 2021;177(4):333–340. doi: 10.1016/J.NEUROL.2020.06.010
35. Keckarević D, Stević Z, Keckarević-Marković M, et al. A novel P66S mutation in exon 3 of the SOD1 gene with early onset and rapid progression. *Amyotroph Lateral Scler*. 2012;13(2):237–240. doi: 10.3109/17482968.2011.627588
36. Kawamata J, Shimohama S, Takano S, et al. Novel G16S (GGC-AGC) mutation in the SOD-1 gene in a patient with apparently sporadic young-onset amyotrophic lateral sclerosis. *Hum Mutat*. 1997;9(4):356–358. doi: 10.1002/(SICI)1098-1004(1997)9:4<356::AID-HUMU9>3.0.CO;2-3
37. Alexander MD, Traynor BJ, Miller N, et al. "True" sporadic ALS associated with a novel SOD-1 mutation. *Ann Neurol*. 2002;52(5):680–683. doi: 10.1002/ANA.10369
38. Al-Chalabi A, Andersen PM, Chioza B, et al. Recessive amyotrophic lateral sclerosis families with the D90A SOD1 mutation share a common founder: evidence for a linked protective factor. *Hum Mol Genet*. 1998;7(13):2045–2050. doi: 10.1093/HMG/7.13.2045
39. Zinman L, Liu HN, Sato C, et al. A mechanism for low penetrance in an ALS family with a novel SOD1 deletion. *Neurology*. 2009;72(13):1153–1159. doi: 10.1212/01.WNL.0000345363.65799.35
40. Абрамычева Н.Ю., Лысогорская Е.В., Шпилюкова Ю.С. и др. Молекулярная структура бокового амиотрофического склероза в российской популяции. *Нервно-мышечные болезни*. 2016;6(4):21–27. Abramycheva NYu, Lysogorskaya EV, Shpilyukova YuS, et al. Molecular structure of amyotrophic lateral sclerosis in Russian population. *Neuromuscular Diseases*. 2016;6(4):21–27. doi: 10.17650/2222-8721-2016-6-4-21-27
41. Renaud L, Picher-Martel V, Codron P, et al. Key role of UBQLN2 in pathogenesis of amyotrophic lateral sclerosis and frontotemporal dementia. *Acta Neuropathol Commun*. 2019;7(1):103. doi: 10.1186/S40478-019-0758-7/TABLES/2
42. Picher-Martel V, Brunet F, Dupré N, et al. The Occurrence of FUS mutations in pediatric amyotrophic lateral sclerosis: a case report and review of the literature. *J Child Neurol*. 2020;35(8):556–562. doi: 10.1177/0883073820915099
43. Naumann M, Peikert K, Günther R, et al. Phenotypes and malignancy risk of different FUS mutations in genetic amyotrophic lateral sclerosis. *Ann Clin Transl Neurol*. 2019;6(12):2384–2394. doi: 10.1002/ACN3.50930
44. Dodd KC, Power R, Ealing J, et al. FUS-ALS presenting with myoclonic jerks in a 17-year-old man. *Amyotroph Lateral Scler Frontotemporal Degener*. 2019;20(3-4):278–280. doi: 10.1080/21678421.2019.1582665
45. Leblond CS, Webber A, Gan-Or Z, et al. De novo FUS P525L mutation in Juvenile amyotrophic lateral sclerosis with dysphonia and diplopia. *Neurol Genet*. 2016;2(2):e63. doi: 10.1212/NXG.0000000000000063
46. Nakaya T, Maragkakis M. Amyotrophic lateral sclerosis associated FUS mutation shortens mitochondria and induces neurotoxicity. *Sci Rep*. 2018;8(1):15575. doi: 10.1038/s41598-018-33964-0
47. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*. 2017;377(2):162–172. doi: 10.1056/NEJMRA1603471
48. Chiò A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler*. 2009;10(5-6):310–323. doi: 10.3109/17482960802566824
49. Westeneng HJ, Debray TPA, Visser AE, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *Lancet Neurol*. 2018;17(5):423–433. doi: 10.1016/S1474-4422(18)30089-9
50. Zou ZY, Liu MS, Li XG, et al. Mutations in SOD1 and FUS caused juvenile-onset sporadic amyotrophic lateral sclerosis with aggressive progression. *Ann Transl Med*. 2015;3(15):221. doi: 10.3978/J.ISSN.2305-5839.2015.09.04

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