Identification of Two Novel Compound Heterozygous ALS2 Mutations in Polish Siblings with Infantile-onset Ascending Spastic Paralysis (IAHSP)

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A – research concept and design, B – collection and assembly of data, C – data analysis and interpretation, D – writing the article, E – critical revision of the article, F – final approval of article

DOI: 10.26399/rmp.v30.3.2024/m.matlawska/i.stepniak/e.elert-dobkowska/k.a.pesz/a.sulek

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ABSTRACT

Identification of Two Novel Compound Heterozygous* ALS2 *Mutations in Polish Siblings with Infantile-onset Ascending Spastic Paralysis (IAHSP)

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Hereditary spastic paraplegias (HSP) represent a group of neurodegenerative disorders with a highly heterogeneous background, thus requiring a multidisciplinary approach in diagnostic procedures. The aim of this study was to identify the genetic basis of familial, severe spastic tetraparesis of unknown etiology in a 26-year-old patient and her younger sister with symptoms of progressive spasticity. Next Generation Sequencing (NGS), Sanger sequencing, and a detailed analysis of segregation of selected variants in family members enabled the identification of two previously undescribed pathogenic mutations in the ALS2 gene in the proband: c.3145T>G and c.3248+5del, in a compound heterozygous configuration. These mutations are responsible for infantile-onset ascending spastic paraplegia (IAHSP) with autosomal recessive inheritance. The analysis of phenotype-genotype correlation allowed differentiation of the siblings' clinical picture from two other clinical phenotypes associated with the occurrence of mutations in the ALS2 gene: juvenile amyotrophic lateral sclerosis (JALS/ALS2) and juvenile primary lateral sclerosis (JPLS). This study also highlights the impact of familial segregation analysis of variants selected in two other genes (SACS and MTRFR), which are associated with recessive forms of spastic paraplegias.

Keywords: *ASL2, IAHSP, hereditary spastic paraplegia, HSP, motor neuron disorders*

STRESZCZENIE

Identyfikacja dwóch nowych mutacji w genie* ALS2 *w układzie heterozygotycznym złożonym u polskiego rodzeństwa z wstępującą paraplegią spastyczną o wczesnym początku (IAHSP)

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Dziedziczne paraplegie spastyczne reprezentują grupę chorób neurodegeneracyjnych o bardzo heterogennym charakterze, stąd też postepowanie diagnostyczne wymaga podejścia multidyscyplinarnego. Celem niniejszej pracy była identyfikacja genetycznego podłoża rodzinnej, ciężkiej tetraparezy o nieznanej etiologii u 26-letniej pacjentki oraz jej młodszej siostry z objawami postępującej spastyczności. Sekwencjonowanie nowej generacji (NGS), sekwencjonowanie Sangera oraz szczegółowa analiza segregacji wyselekcjonowanych wariantów wśród członków rodziny pozwoliły na identyfikację dwóch wcześniej nieopisanych, patogennych wariantów w genie ALS2 u probandki: c.3145T>G i c.3248+5del w złożonym układzie heterozygotycznym, odpowiedzialnych za wstępującą paraplegię spastyczną o wczesnym początku (IAHSP), dziedziczoną autosomalnie recesywnie. Analiza korelacji genotyp-fenotyp pozwoliła na zróżnicowanie obrazu klinicznego choroby występującej u rodzeństwa z dwoma innymi fenotypami klinicznymi związanymi z mutacjami w genie ALS2: młodzieńczym stwardnieniem bocznym zanikowym (JALS/ALS2) oraz młodzieńczym pierwotnym stwardnieniem bocznym (JPLS). W pracy podkreślono także wpływ analizy segregacji rodzinnej wybranych wariantów dwóch innych genów (SACS i MTRFR) związanych z występowaniem recesywnych postaci paraplegii spastycznych.

Słowa kluczowe: *ASL2, IAHSP, dziedziczna paraplegia spastyczna, choroby neuronu ruchowego, SPG*

Introduction

Infantile-onset ascending spastic paralysis (IAHSP) belongs to the group of hereditary spastic paraplegias (HSPs) with an autosomal recessive inheritance pattern, associated with mutations in the *ALS2* gene. IAHSP is a very rare neurodegenerative motor neuron disorder (prevalence 1: 1,000,000) with onset before the age of 2 years. It presents with rapidly progressive spasticity and muscle weakness, leading to spastic tetraparesis and bulbar syndrome within the first decade of life, although cognitive functions are preserved [1,2,3,4]. In addition to these symptoms, IAHSP patients may also present with anarthria, dysphagia and chewing difficulties, dystonia, and in some cases, extrapyramidal features and oculomotor abnormalities [5]. Most IAHSP patients require a wheelchair by their first decade, and there is currently no treatment available for motor neuron degeneration in this disease or in other disorders caused by recessive mutations in the *ALS2* gene [1]. Here, we present a case of two sisters with IAHSP and a family history of spastic tetraparesis.

Clinical features

Two sisters, a 26-year-old proband and a 22-year-old sibling, presenting with progressive spastic gait and speech problems, were referred to our genetics outpatient clinic. According to the patients and their oldest living relative, the parents of the affected sisters are unrelated; however, both were born in the same village. Additionally, a woman in an earlier generation on their father's side reportedly had similar symptoms and died at 47 years of age.

The proband was born following an uneventful pregnancy and delivery. Her motor development during the first year was typical, and she began walking independently at 16 months, though she walked on tiptoes. At the age of 4, she underwent lengthening of the Achilles tendon. Neurological assessments up to age 11 revealed spastic paraparesis. Dysarthria developed at age 12, followed by swallowing difficulties, pronounced drooling, and spasticity in the upper limbs by age 14. She exhibited no learning, behavioral, or cognitive difficulties. Symptoms gradually progressed, and by age 17, she lost the ability to walk, eventually losing the ability to write and sit unsupported at age 24. Additionally, patient experienced head control issues, bowel and bladder dysfunction, and required diapers. Furthermore, biochemical and metabolic tests, along with karyotyping conducted in childhood, revealed no abnormalities. Brain MRI at age 15 was normal, but a subsequent MRI 10 years later showed mild atrophy in the frontal and parietal lobes of the cerebral cortex. Nerve conduction studies and electromyography were normal, and no ophthalmologic pathology was noted.

Neurological examination of both patients showed severe spastic tetraplegia with contractures, hyperreflexia, and bilateral Babinski sign. Both sisters had anarthria, with an absence of tongue movements; however, fasciculations and amyotrophy of the tongue and limbs were not observed. Additionally, head dropping was observed in the proband.

Methods

A 26-year-old female patient was referred to the Department of Genetics at the Institute of Psychiatry and Neurology for testing due to suspected progressive hereditary neurodegenerative disease and a positive family history of spastic tetraparesis. Whole blood was collected in EDTA tubes from the proband and her family members: mother, father, brother, and sister. Isolation of genetic material (DNA) from leukocytes was performed using the MagNA Pure processing station by Roche, in line with the manufacturer's protocol. The quality and purity of isolated DNA were verified using a Nanodrop 2000 spectrophotometer (Thermo Scientific). According to the manufacturer's protocol, an initial 50 ng of DNA was used for DNA library preparation, indexing, and sample enrichment. The commercial Illumina TruSight™ One Sequencing Panel (Illumina) was used to cover genes associated with neurodegenerative diseases. This panel covering the coding regions of 4,813 genes associated with known clinical phenotypes. Sequencing was performed using a MiSeq™ Illumina sequencer. The coding regions of 108 genes associated with neurodegenerative diseases (spastic paraplegia, hereditary ataxia, and motor neuron disorders) were analyzed. Data were processed using Illumina VariantStudio 2.2 with the following criteria: (a) ≥20 reads for the gene sequence, (b) variant frequency ≥25%, (c) variant frequency <0.005 in the Exome Aggregation Consortium database (https://exac.broadinstitute.org/), (d) exclusion of deep intronic and synonymous variants from the analysis. The Integrated Genomics Viewer (IGV) was used to visualize detected variants. Bioinformatics analysis was performed using the following databases: SIFT (http://sitf.jcvi.org/), Polyphen 2 (http://genetics.bwh.harvard.edu/pph2/), ClinVar (https://www .ncbi.nlm.nih.gov/clinvar/), Mutation Taster (http://mutationtaster.org/) and dbSNP (https://www.ncbi.nlm.nih.gov/snp/). Because the initial analysis and interpretation of the NGS data were performed before the American College of Medical Genetics and Genomics and Association for Molecular Pathology guidelines were published, the clinical significance and classification of identified variants were based on (i) ClinVar database, (ii) frequency in

the Exome Aggregation Consortium database, and (iii) MutationTaster predictions. Selected variants corresponding to the spectrum of proband's symptoms were confirmed by Sanger sequencing. Sanger sequencing of selected amplicons was also performed on family members of the proband to analyze the segregation of individual variants within the family.

The reanalysis of data was conducted according to the Standards and Guidelines for the Interpretation of Sequence Variants recommended by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Current interpretation is also based on the GnomAD population frequency data.

Results

Next Generation Sequencing (NGS) analysis of 108 genes related to spastic paraplegias, hereditary ataxias, and motor neuron disorders led to the identification of variants in three genes: *ALS2*, *MTRFR* (previously *C19orf65*), and *SACS*.

In the proband and her younger sister, two recessive mutations (missense and deletion) – c.3145T>G and c.3248+5del – were identified in the *ALS2* gene (2q33-q35) in a compound heterozygous pattern. Due to the lack of identified variants in the population study and predictive algorithms, both identified variants were classified as probably pathogenic and in this biallelic pattern constitute the genetic basis of the clinical phenotype of the proband and her sister. Segregation analysis of the *ALS2* gene variants among family members revealed that they are located on two alleles: the proband's mother was an asymptomatic carrier of the c.3145T>G missense mutation in the *ALS2* gene, while the father was an asymptomatic carrier of the c.3248+5del deletion in the same gene. The proband's brother did not have an abnormal variant on either allele.

Segregation analysis of two variants identified during the NGS study in the *SACS* gene – c.696T>A p.(Asn232Lys) and c.11032C>G p.(Pro3678Ala) – showed that the proband, her sister, and her brother were compound heterozygotes for the detected variants. The mother was homozygous for the c.696= variant, while the c.11032C>G variant occurred in a heterozygous pattern. The father was heterozygous for the c.696T>A variant and homozygous for the c.11032C>G variant. Based on the homozygosity status in the parents and their presence in the healthy population, the *SACS* gene variants were classified as benign, and their influence on the clinical presentation of the proband and her affected sister was excluded.

The c.44G>A p.(Arg15Gln) missense variant in the *MTRFR* (previously known as *C12orf65*) gene, detected during NGS analysis, was identified in the proband in a homozygous pattern. Segregation analysis of the variant in the family showed that the remaining family members were heterozygous for the detected mutation. Since the proband's sister was heterozygous for the *MTRFR* variant, which was also reported in population studies, the c.44G>A variant in the *MTRFR* gene was classified as benign. Furthermore, a detailed analysis of clinical data excluded any impact of the *MTRFR* gene variant on the phenotype presented by the patient and her sister.

Table 1. Genotypes of family members for three identified genes

Family member	**Gene / exon**									
	NM_020919.4				**NM_014363.6**				**NM_152269.5**	
	***ALS2* exon 18**		***ALS2* exon19**		***SACS* exon 8**		***SACS* exon10**		***MTRFR* (previously C12orf65) exon 2**	
	allele 1	allele 2	allele 1	allele 2	allele 1	allele2	allele 1	allele 2	allele 1	allele 2
Proband	**c.3145T>G**	c.3145=	**c.3248+5delG**	c.3248+5=	c.696T>A	c.696T=	c.11032C>G	c.11032C=	c.44G>A	c.44G>A
Mother	c.3145T>G	c.3145=	c.3248+5=	c.3248+5=	c.696T=	c.696T=	c.11032C>G	c.I1032C=	c.44G>A	c.44G=
Father	c.3145=	c.3145=	c.3248+5delG	c.3248+5=	c.696T>A	c.696T>A	c.11032C=	c.11032C=	c.44G>A	c.44G=
Sister	**c.3145T>G**	c.3145=	**c.3248+5delG**	c.3248+5=	c.696T>A	c.696T=	c.11032C>G	c.11032C=	c.44G>A	c.44G=
Brother	c.3145=	c.3145=	c.3248+5=	c.3248+5=	c.696T>A	c.696T=	c.11032C>G	c.11032C=	c.44G>A	c.44G=

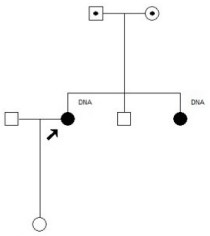

Figure 1. Pedigree of the family with spastic tetraparesis cases

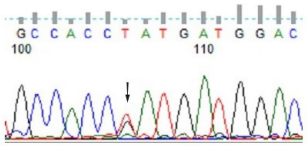

Figure 2. Missense mutation c.3145T>G in 18. exon of the *ALS2* gene

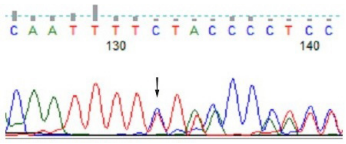

Figure 3. Deletion c.3248+5delG in 19. exon of the *ALS2* gene

Discussion

Hereditary spastic paraplegias (HSPs) are a group of clinically diverse and genetically heterogeneous neurodegenerative disorders. To date, over 80 gene loci associated with HSPs have been described [6,7]. The multitude of genes involved in the pathogenesis of individual types of HSP and the various types of inheritance (AD, AR, XLR, mitochondrial) effectively hinder a clear genotype-phenotype correlation [8]. Spastic paraplegia can present in either a pure or complex form [9]. In the complex form of HSP, additional neurological symptoms are observed, i.e., muscle atrophy, peripheral neuropathy, varicose veins, seizures, extrapyramidal dysfunction, dysarthria, visual atrophy, ataxia, intellectual disorders, cognitive impairment, and gastroesophageal reflux [6,10]. Mutations in the *ALS2* gene are associated with three recessive clinical phenotypes of spastic paraplegia: the previously mentioned infantile-onset ascending spastic paralysis (IAHSP), juvenile primary lateral sclerosis (JPLS), and juvenile amyotrophic lateral sclerosis (JALS/ALS2). The genetic background of IAHSP involves mutations in the *ALS2* gene (2q33-q35), which encodes alsin. This protein may exist in two isoforms: alternative splicing produces a longer transcript encoding a protein with 1,657 amino acids (NP_065970.2) and a shorter one encoding 396 amino acids (NP_001129217.1). Both isoforms are present in motor neurons, among other cells. The longer transcript consists of 34 exons and encodes a functional protein, while the shortened transcript contains only exons 1-4 and has an open reading frame [11]. It is likely that the shortened transcript is not translated, or that its protein product is rapidly degraded in cells. The structure of alsin and the mechanism of interaction with other proteins are not fully understood. Experimental evidence supports the hypothesis that this protein functions as a regulator of GTPases, regulating, among others, growth and survival of spinal cord motor neurons in mammals by reorganizing the cytoskeleton and participating in endocytosis [1,12]. Experimental studies suggest that alsin is involved in modulating the activity of AMPA receptors through interaction with GRIP1, which may prevent excitotoxicity [1,13]. Other studies have shown that overexpression of alsin and direct interaction with mutated SOD1 can have a neuroprotective effect on motor neurons by inhibiting toxicity induced by SOD1 gene mutations; however, in vivo studies have not yet been performed [12]. An experiment by Tudor et al. (2005) demonstrated that alsin regulates neurite outgrowth through interaction of the alsin DH/PH domain with Rho, Rac, and Cdc42 regulators, thereby activating the Rac1-PAK1 pathway, which is responsible for the growth of axons and neurites [14]. Most mutations in the alsin gene are predicted to cause early protein truncation and the absence of one of the domains (VPS9), which functions as a guanine exchange factor (GEF) for RAB5 GTPase. RAB5 acts as a key regulator of endocytosis during endosome fusion and trafficking [8]. Both compound heterozygous variants identified in this study localize to the part of the protein where MORN (membrane occupation and recognition nexus) repeats are present. The MORN repeat is identified in multiple copies across various proteins, including junctophilins [15]. These repeats are found in association with a wide range of other domains and are thought to act as lipid-binding modules [16]. There are eight MORN repeats in *ALS2*. At present, it is difficult to explain how the localization of variants in the MORN repeats influences the pathology of the alsin protein and the infantile-onset ascending spastic paraplegia phenotype.

In the proband, a total of five variants were detected in three genes associated with recessive spastic paraplegias, inherited in a compound heterozygous pattern in two genes (variants in exons 18 and 19 of the *ALS2* gene and variants in exons 8 and 10 of the *SACS* gene) and a homozygous variant in exon 2 of the *MTRFR* gene. Next Generation Sequencing, analysis, and classification of detected variants were performed in 2015, prior to the publication of the American College of Medical Genetics and Genomics & Association for Molecular Pathology (ACMGG & AMP) guidelines.

Therefore, great emphasis was placed on sequencing selected amplicons using the Sanger method and analyzing the segregation of individual variants in the family. Through this and reanalysis following the newly published ACMGG & AMP Guidelines, it was determined that the genetic basis of the disease in the proband and her sister involves two recessive pathogenic mutations in the *ALS2* gene, located on two alleles: c.3145T>G p.(Tyr1049Asp) and 3248+5del. These mutations have not been previously described in bioinformatics databases, nor were they found in a cohort of 41 patients at the Institute of Psychiatry and Neurology who suffer from neurological diseases.

Additionally, at the age of 24, the proband gave birth to a healthy girl following an uneventful pregnancy and a delivery through caesarean section. The proband and her sister shared identical symptoms: toe-walking in early childhood, anarthria with lack of tongue movement, swallowing difficulties, and progressive severe spastic tetraplegia with contractures, hyperreflexia, and a bilateral Babinski sign.

Reaching a clear diagnosis in cases of infantile ascending spastic paralysis is challenging due to several factors: (1) the very limited number of cases described worldwide, based on studies of only local cohorts, (2) the structure and function of alsin are not fully understood, as well as the correlation of mutations in specific regions of its domains with disease progression and symptom onset, and (3) the absence of a multidisciplinary network to enable the rapid exchange of information regarding early-onset *ALS2* from clinical, cellular, and molecular perspectives. Thus, despite differences in clinical presentation, IHASP is difficult to distinguish from two other early-onset phenotypes associated with the *ALS2* gene: juvenile amyotrophic lateral sclerosis (JALS/ALS2) and juvenile primary lateral sclerosis (JPLS). To date, no specific mutations have been identified to differentiate these diseases based on a characteristic clinical phenotype or symptom severity, as in adult amyotrophic lateral sclerosis (ALS) [17,18].

The heterogeneous genetic background also complicates prediction of early-onset ALS progression, which can range from a slow course to a very aggressive one, sometimes ending in death within a few years of symptom onset [19]. The course of JPLS is very similar to IAHSP; studies of an Egyptian cohort of 26 patients suggested that JPLS may represent a continuation of IAHSP, with the two phenotypes forming a single disease entity without a genotype-phenotype correlation [20]. However, one of the potentially specific symptoms that may distinguish JPLS is a saccadic movement disorder, which is particularly troublesome when trying to look down [1]. No saccadic movement disorders were observed in our patients. The prognosis for survival in both disorders is generally favorable, but complete immobilization in the final phase of IAHSP/JPLS significantly reduces the patient's quality of life.

Juvenile amyotrophic lateral sclerosis (JALS/ALS2) is characterized by an age of onset under 25 years, with upper motor neuron involvement. Notably, no mutations in the *C9orf72* gene, which is most commonly involved in pathogenesis of adult amyotrophic lateral sclerosis (ASL), have been described in JALS/ALS2 [21]. In JALS patients, involvement of both upper and lower motor neurons is observed, resulting in muscle weakness and spasticity, often includes facial muscle spasticity, bladder muscle dysfunction, dysarthria with uncontrolled bursts of laughter, cases with intellectual disability, and severe scoliosis [22]. Mutations in several other genes may contribute to JALS/ALS2, including *SETX*, *FUS*, *UBQLN2*, *SPG11*, and *SIGMAR1*. Mutations in the *FUS* gene, in particular, account for most sporadic cases of JALS [1,23].

Considering the very early childhood onset of symptoms and the occurrence of severe spastic tetraparesis before age 25, along with new studies indicating that JPLS may represent a continuation of IAHSP, we arrived at this diagnosis for our patients [24,20]. Additionally, since hereditary spastic paraplegias (HSPs) encompass a group of clinically diverse and genetically heterogeneous neurodegenerative diseases with varying ages of onset, symptom severity, and survival estimates, all of which share the feature of progressive spasticity and muscle weakness, a diagnosis of IAHSP should involve particular attention to the familial segregation of gene variants associated with other recessive forms of spastic paraplegia, as demonstrated in the case described above [25].

References

1. Miceli M., Exertier C., Cavaglià M. et al.: ALS2-Related Motor Neuron Diseases: From Symptoms to Molecules. Biol (Basel) 2022; 11(1): 77. doi: 10.3390/biology11010077. PMID: 35053075; PMCID: PMC8773251.
2. Orphanet: Disease search simple. Available at: https://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=PL (accessed 13.07.2024).
3. Eker H.K., Unlü S.E., Al-Salmi F. et al.: A novel homozygous mutation in ALS2 gene in four siblings with infantile-onset ascending hereditary spastic paralysis. Eur J Med Genet 2014; 57(6): 275-278. doi: 10.1016/j.ejmg.2014.03.006. PMID: 24704789.
4. Eltoum A., O'Rourke D., Sharif F.: Infantile onset ascending hereditary spastic paralysis. BMJ Case Rep 2022; 15(1): e240941. doi: 10.1136/bcr-2020-240941. PMID: 35039335; PMCID: PMC8767962.
5. Madhaw G., Kumar N.M., Radhakrishnan D. et al.: Infantile Ascending Hereditary Spastic Paralysis with Extrapyramidal and Extraocular Manifestations Associated with a Novel ALS2 Mutation. Mov Disord Clin Pract 2021; 9(1): 118-121. doi: 10.1002/mdc3.13372. PMID: 35005076; PMCID: PMC8721836.
6. Meyyazhagan A., Orlacchio A.: Hereditary Spastic Paraplegia: An Update. Int J Mol Sci 2022; 23(3): 1697. doi: 10.3390/ijms23031697. PMID: 35163618; PMCID: PMC8835766.

7. Murala S., Nagarajan E., Bollu P.C.: Hereditary spastic paraplegia. Neurol Sci 2021; 42(3): 883-894. doi: 10.1007/s10072-020-04981-7. PMID: 33439395.
8. Racis L., Tessa A., Pugliatti M. et al.: Infantile-onset ascending hereditary spastic paralysis: a case report and brief literature review. Eur J Paediatr Neurol 2014; 18(2): 235-239. doi: 10.1016/j.ejpn.2013.09.009. PMID: 24144828.
9. Ikeda A., Kumaki T., Tsuyusaki Y. et al.: Genetic and clinical features of pediatric-onset hereditary spastic paraplegia: a single-center study in Japan. Front Neurol 2023; 14: 1085228. doi: 10.3389/fneur.2023.1085228. PMID: 37251230; PMCID: PMC10213624.
10. Shi Y., Wang A., Chen B. et al.: Clinical Features and Genetic Spectrum of Patients With Clinically Suspected Hereditary Progressive Spastic Paraplegia. Front Neurol 2022; 13: 872927. doi: 10.3389/fneur.2022.872927. PMID: 35572931; PMCID: PMC9097539.
11. Sprute R., Jergas H., Ölmez A. et al.: Genotype-phenotype correlation in seven motor neuron disease families with novel ALS2 mutations. Am J Med Genet A 2021; 185(2): 344-354. doi: 10.1002/ajmg.a.61951. PMID: 33155358.
12. Hadano S., Kunita R., Otomo A. et al.: Molecular and cellular function of ALS2/alsin: implication of membrane dynamics in neuronal development and degeneration. Neurochem Int 2007; 51(2-4): 74-84. doi: 10.1016/j.neuint.2007.04.010. PMID: 17566607.
13. Cai H., Shim H., Lai C. et al.: ALS2/alsin knockout mice and motor neuron diseases. Neurodegener Dis 2008; 5(6): 359-366. doi: 10.1159/000151295. PMID: 18714162; PMCID: PMC2556598.
14. Tudor E.L., Perkinton M.S., Schmidt A. et al.: ALS2/Alsin regulates Rac-PAK signaling and neurite outgrowth. J Biol Chem 2005; 280(41): 34735-34740. doi: 10.1074/jbc.M506216200. PMID: 16049005.
15. Takeshima H., Komazaki S., Nishi M. et al.: Junctophilins: a novel family of junctional membrane complex proteins. Mol Cell 2000; 6(1): 11-22. doi: 10.1016/s1097-2765(00)00003-4. PMID: 10949023.
16. Sajko S., Grishkovskaya I., Kostan J. et al.: Structures of three MORN repeat proteins and a re-evaluation of the proposed lipid-binding properties of MORN repeats. PLoS One 2020; 15(12): e0242677. doi: 10.1371/journal.pone.0242677. PMID: 33296386; PMCID: PMC7725318.
17. Lehky T., Grunseich C.: Juvenile Amyotrophic Lateral Sclerosis: A Review. Genes (Basel) 2021; 12(12): 1935. doi: 10.3390/genes12121935. PMID: 34946884; PMCID: PMC8701111.
18. Tariq H., Mukhtar S., Naz S.: A novel mutation in ALS2 associated with severe and progressive infantile onset of spastic paralysis. J Neurogenet 2017; 31(1-2): 26-29. doi: 10.1080/01677063.2017.1324441. PMID: 28502191.
19. Bodur M., Toker R.T., Başak A.N. et al.: A rare case of juvenile amyotrophic lateral sclerosis. Turk J Pediatr 2021; 63(3): 495-499. doi: 10.24953/turkjped.2021.03.017. PMID: 34254495.
20. Zaki M.S., Sharaf-Eldin W.E., Rafat K. et al.: Clinical and molecular spectrum of a large Egyptian cohort with ALS2-related disorders of infantile-onset of clinical continuum IAHSP/JPLS. Clin Genet 2023; 104(2): 238-244. doi: 10.1111/cge.14338. PMID: 37055917.
21. Sánchez-Tejerina D., Restrepo-Vera J.L., Rovira-Moreno E. et al.: An Atypical Presentation of Upper Motor Neuron Predominant Juvenile Amyotrophic Lateral Sclerosis Associated with TARDBP Gene: A Case Report and Review of the Literature. Genes (Basel) 2022; 13(8): 1483. doi: 10.3390/genes13081483. PMID: 36011394; PMCID: PMC9407925.
22. Siddiqi S., Foo J.N., Vu A. et al.: A novel splice-site mutation in ALS2 establishes the diagnosis of juvenile amyotrophic lateral sclerosis in a family with early onset anarthria and generalized dystonias. PLoS One 2014; 9(12): e113258. doi: 10.1371/journal.pone.0113258. PMID: 25474699; PMCID: PMC4256290.
23. 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. PMID: 33036763.
24. Helal M., Mazaheri N., Shalbafan B. et al.: Clinical presentation and natural history of infantile-onset ascending spastic paralysis from three families with an ALS2 founder variant. Neurol Sci 2018; 39(11): 1917-1925. doi: 10.1007/s10072-018-3526-8. PMID: 30128655.
25. Eymard-Pierre E., Lesca G., Dollet S. et al.: Infantile-onset ascending hereditary spastic paralysis is associated with mutations in the alsin gene. Am J Hum Genet 2002; 71(3): 518-527. doi: 10.1086/342359. PMID: 12145748; PMCID: PMC379189.

Funding: This study was partially supported by internal statutory grant IPIN-16202 (Polish Ministry of Education and Science).

Acknowledgments: This study was approved by Bioethics Committee of the Institute of Psychiatry and Neurology in Warsaw, resolution number 13/2016.

The authors declare no conflict of interest.

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