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ORIGINAL ARTICLE

Phenotypic and genotypic features of patients diagnosed with ALS in the city of Sakarya, Turkey

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease leading to motor neuron damage. In this study, the clinical, demographic, and genetic features of ALS patients in the city of Sakarya, Turkey, were investigated. Patients with an established diagnosis of ALS according to the Awaji criteria were included. Age, sex, age at onset of ALS, initial complaints, consanguineous marriage, and genetic features were retrospectively investigated. Conventional genetic analysis and NGS were used for molecular evaluation of patients. A total of 55 probands (10 familial, 45 sporadic) in whom ALS was suspected due to their phenotypic features were included. Thirty-two patients were male (58.2%), and 23 were female (41.8%); their mean ages were 62.65 ± 13 years. The mean age of onset for 37 familial patients from 10 families was 49.9 years. Two cases had juvenile-onset. Fourteen (25.5%) bulbar-onset versus 40 (72.7%) limb-onset patients were detected; one patient had both. Six (10.9%) patients showed marked frontotemporal dementia. Twenty-nine (52.7%) patients died during the follow-up period. Genetic analysis identified causative variants in eleven cases, carrying variants in six different ALS genes (*C9orf72*, *SOD1*, *VCP*, *SPG11*, *TBK1, and SH3TC2*). Genetic investigations have revealed more than 40 genes to be involved in the pathogenesis of ALS. Our relatively small study cohort restricted to one province of Turkey, however, prone to migration, consists of 10/55 familial ALS cases, which harbor two rare (*SH3TC2*-p.Met523Thr and TBK1-p.Glu643del) and two novel (SPG11-p.Lys656Valfs*11 and VCP-p.Arg191Pro) mutations contributing to the literature.

Keywords Amyotrophic lateral sclerosis · Familial · Sporadic · Genetic analysis · Sakarya district · Turkey

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects motor neurons in the cortex, brain stem, and spinal cord. The prevalence of ALS ranged from 1.07–11.31 per 100.000 in meta-analysis of twenty-six different studies [1]. Most of study suggested a slightly increasing prevalence of ALS over years [2, 3]. The prevalence of ALS appears to vary between ethnic groups. The prevalence of European American ALS is higher than African American ALS patients (5.4:2.3) [4]. A study reported that the prevalence was 7.3 per 100.000 in Thrace region of Turkey [5].

Chiò et al. reported that the incidence rate was 2, Ryan et al. reported 3.1 per 100.000 individuals [6, 7]. When the disease was evaluated according to gender, male sex has since long being considered a risk factor for ALS. The studies reported that male-to-female ratios in ALS between 1.2 and 1.5 [8, 9]. If no family history is identified, the diagnosis is assumed to be sporadic. The sporadic ALS comprises 67% males [10]. In familial ALS, ratio of males to females is 1:1 [10]. A study reported that the mean male-specific annual incidence was 1.8, and female-specific was 1.3 per 100.000/year [7]. A prospective population-based parent–offspring heritability study was reported that the

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annual age-standardized and sex-standardized incidence of ALS did not change with time [7]. Most studies detected that the incidence of sporadic was 1–2 per 1000.000 individuals, years ALS in the Western countries [11–13].

ALS has a complex genetic origin. Heritability measures the extent to which genetic variation between individuals. Family history of ALS in a first degree relatives increases the risk of developing ALS 1.4-fold.[7]. A study reported that if there was no family history of ALS, the mean lifetime heritability was 36.9% [7].

ALS increases exponentially with age. Sporadic ALS usually occurs in mid-to-late 50 s [10]. The age of onset for sporadic ALS is 58–63 [14, 15]. A peak incidence in the age group 70–74 years [16]. About 10–15% of the disease has a familial ALS form occurs in patients in their late teens or early adulthood [10]. A study reported that affected offspring were younger than their parents in assessment using parent–child ALS dyads [7].

ALS patients have a more limited survival after diagnosis. A slow form of ALS with a survival of 10 years or longer is seen in 10% of the patients.

The pathophysiology of ALS is characterized by the loss of pyramidal Betz cells (motor cortex) as well as by loss and degeneration of the large anterior horn cells (spinal cord and lower cranial motor nuclei of the brainstem) [17]. Damaged motor neurons display intracellular aggregates that form distinct ubiquitinated inclusions, which play an important role in the pathology of the disease. There is no single or specific test for ALS diagnosis. Diagnosis is established by proving the presence of a progressive disorder with manifestations of typical upper and lower motor neuron involvement and exclusion of other etiologies by clinical examination and electromyography [13, 18, 19]. The Awaji criteria are used for diagnosis and classification [20]. The Awaji criteria recommended that neurophysiological data should be used in the context of clinical information. In addition, fasciculation potentials associated with signs of reinnervation were considered as evidence of lower motor neuron lesion, in particular in cranial-innervated or strong limb muscles.

Over the last decade, genetic discoveries had a profound impact on our understanding of ALS and there was an exponential growth in the phenotypes labeled as ALS. ALS is now considered not as a single disease, but rather as a syndrome, consisting of diseases due to a series of non-overlapping mechanisms, which, however, all culminate in motor neuron death. Genetics has provided novel insights into the pathogenesis of ALS, yet also uncovered novel layers of complexity, increasingly influencing diagnostics and treatment. Today, more than 40 genes are implicated in the pathogenesis of ALS, which can be summed up in three main groups as disrupted protein homeostasis, impaired RNA metabolism, and axonal transport defects [21]. Protein aggregates are a hallmark of several neurodegenerative diseases. Thus, misfolded SOD1 aggregates and other defective genes' products like UBQLN2, VCP, OPTN, and TBK1, involved in ubiquitin-proteosome system, ER-mediated degradation, and autophagy have been the main focus of ALS research. However, identification of mutations in RNA-binding proteins TDP-43 and FUS has associated the defects in RNA processing with ALS pathology. TDP-43 protein inclusions are observed in motor neurons of all ALS cases, with the exception SOD1 and FUS-based ALS. In case of ALS, TDP-43 and FUS, normally located in the nucleus, are exported to cytoplasm and cause formation of stress granules, which sequester several RNA-binding proteins, silencing mRNA translation. Moreover, disrupted RNA metabolism in ALS is further supported by the formation of nuclear and cytoplasmic RNA foci that harbor RNA–protein aggregates as a result of the dynamic hexanucleotide repeat expansions in the promoter region of *C9orf72*, which is the most frequent genomic variation both in fALS and in sALS worldwide. Finally, altered cytoskeletal dynamics, due to pathogenic variations in several proteins involved in axonal integrity and transport (e.g., PFN1, DCTN1, NEFH and TUBA4A), is the third main pathology underlying ALS.

Most ALS cases are sporadic, with the exception of 10% showing hereditary patterns [21, 22]. Sporadic ALS (sALS) is considered to be a result of the involvement of genetic and environmental factors; its etiology is not yet known. Familial ALS, although low in percentage, is a model to study sALS, since the pathological signs of the familial and sporadic disease exhibit great similarity. However, even fALS is phenotypically and genetically heterogeneous. In the majority of fALS cases, an autosomal dominant inheritance pattern has been described, although recessive and X-linked forms also exist [23]. In addition, the Mendelian inheritance of ALS indicates that the genetic defects expressed become selectively toxic, indicating incomplete penetrance. This, in turn, suggests a significant role for genetic factors in the sporadic form of ALS. Twelve percent of fALS cases are explained with *SOD1* mutations, 4–5% with *FUS* and *TARDBP* each, and 40% with *C9orf72* [24–27]. These are followed by *ANG*, *OPTN*, *UBQLN2*, and *VCP* [21, 23]. These same gene mutations explain approximately 12% of sporadic cases.

Clinical and pathological findings of fALS and sALS cases are indistinguishable, with the exception of the age at onset being several years earlier in fALS. Genetic transmission is usually autosomal dominant with various penetrance ratios in fALS [20, 28]. To predict the clinical course and prognosis of ALS, genotyping is important. Next-generation sequencing (NGS) has made a great impact on our progress toward the genetic diagnosis of neurological disorders. Especially whole exome sequencing (WES) has been applied both in research and in diagnostic settings, using single cases or case–control studies with thousands of subjects to identify novel disease-causing genes. Currently, the diagnostic

success rate of WES is approximately 40%, which can be higher in familial cases and in consanguineous families [29]. In this study, we investigated the phenotypic and genotypic features of ALS cases in Sakarya, Turkey, using conventional and next-generation sequencing methods.

Materials and methods

We reviewed the clinical findings and genetic analyses of 55 patients, who were diagnosed with ALS in our center between June 2012 and March 2019. Brain and spinal MRI and electrophysiological tests were performed in all patients to diagnose the disease. The patients' initial symptoms (bulbar, upper limb, lower limb-onset) were recorded. Physical examination findings, including a detailed neurological examination, dysmorphic features, and course of the disease were evaluated. Further, consanguineous marriage and the presence of similar diseases within the family were recorded and clinical phenotypes were categorized. Pedigree analysis pointed to genetic transmission in several cases. For a definitive diagnosis samples were subjected to genetic analyses and peripheral venous blood samples obtained from patients and family members were investigated. Genomic DNA was extracted from whole blood using the MagNAPure Compact DNA Isolation System (Roche, Switzerland). Conventional screening of the most common ALS genes (*SOD1*, *TARDBP (exon 5)*, *FUS* (exons 14 and 15) and *UBQLN2*) was performed using polymerase chain reaction (PCR) followed by Sanger sequencing (Macrogen, Korea). The hexanucleotide repeat expansion in the promoter region of the *C9orf72* genewas tested using repeat-primed PCR and fragment length analysis. WES coupled with bioinformatic analysis was performed in a subset of unsolved cases. Segregation analysis for the candidate variants was performed in available family members. The patients with spinobulbar muscular atrophy were excluded. Twenty-five sALS samples were subjected to whole genome sequencing (WGS) in the framework of Project MinE.

Results

The demographic features of 55 ALS patients included in this study are compiled in Table 1. The patients were divided into three groups according to Awaji criteria: definite ALS (74.5%), probable ALS (18.2%), and possible ALS (7.3%).

Except for two cases with juvenile-onset, the mean age of onset of the patients was 60.75 ± 10.25 years, and the mean age at the time of onset of disease complaints was 57.94 ± 14.41 years. In the two juvenile cases, complaints started at the ages of 17 and 20. The study included 37 fALS patients from 10 (18.2%) families and 45 (81.8%) sALS cases (Table 1). The mean age at onset was 49.9 (17–77) years for fALS (Table 2). Two (3.6%) sALS patients were 80 years or older at disease onset. Fourteen (25.5%) bulbar-onset ALS patients were detected and all of them were sALS. Among 40 (72.7%) patients with limb-onset disease, 18 had lower (13 sALS, 5 fALS), 21 had upper (16 sALS, 5 fALS) extremity symptoms, and one patient showed both. Only one patient in our study cohort had bulbar and upper extremity symptoms at the same time, as an initial symptom of ALS (Table 1). A patient with bulbar-onset had weakness of neck flexor muscles as a rare symptom of ALS. The patient had additional findings including thenar–hypothenar atrophy, hyperactive deep tendon reflexes, and weakness three months later. Myasthenia graves were excluded by negative anti-acetylcholine receptor antibody, no response to edrophonium test, no abnormality in repetitive nerve stimulation, and single-fibre electromyography. He had normal value of creatinine kinase. Clinical and control electrophysiological study confirmed ALS diagnosis after three months.

Muscle atrophy was observed in all subjects, but the distribution of the atrophy was wide in four patients. These patients had bilateral flail arm syndrome also known as 'man-in-barrel syndrome' in clinical follow-up after the diagnosis. Six (10.9%) ALS patients showed overtly frontotemporal dementia (FTD) (4 sALS, 2 fALS).

During the follow-up period, twenty-nine (52.7%) patients died. Most of these patients deceased from respiratory failure, the cause of death could not be determined in some other patients. The diaphragm pacing system was applied to two patients. One patient lived for 3 years after application of the diaphragm pacing system, another patient had diaphragm pacing system for a 1 year.

Genetic analysis identified causative variants in 20% of cases in the cohort under study (11/55) (Table 2). The C9orf72 hexanucleotide repeat expansion was detected in six ALS cases (10.9%). Four of these cases had fALS and two were sporadic. Three female and three male patients were recorded. The mean age of disease onset of *C9orf72* expansion carriers was 57 (53–62) years. One of them had bulbar-onset, the others had limb-onset. Dementia was not observed among our C9orf72 mutation carriers.

The heterozygous *SOD1*-p.Asn87Ser mutation was detected in a sporadic male patient with limb-onset (upper extremity) disease. The age of symptom onset was 48. The patient had man-in-barrel syndrome. Healthy sibs (five sisters and two brothers) and the healthy mother did not carry this variant. The father who died at a car accident at the age of 50 could not be tested; however, he is most probably the transmitter of the variant.

Causative variants are identified in all four fALS cases analyzed by whole exome sequencing. In a family with six affected members (father, four sisters, and nephew), a novel *VCP* mutation (c.572G > C p.Arg191Pro, NM_007126) was

Table 1 Clinical features and findings of patients' sporadic ALS and familial ALS groups

	Sporadic ALS *n* (percentage)	Familial ALS *n* (percentage)	Total *n* (percentage)
Gender			
Male	27 (49.1%)	5 (9.1%)	32 (58.2%)
Female	18 (32.7%)	5 (9.1%)	23 (41.8%)
Age			
Juvenil-onset (≤ 20 year)	1 (1.8%)	1 (1.8%)	2 (3.6%)
Adult-onset (21–79)	42 (76.4%)	7 (12.7%)	49 (89.1%)
Elderly-onset (≥ 80 year)	2 (3.6%)	2 (3.6%)	4 (7.3%)
Awaji criteria			
Definite	33 (60%)	8 (14.5%)	41 (74.5%)
Probable	10 (18.2%)	0	10 (18.2%)
Possible	2 (3.6%)	2 (3.6%)	4 (7.3%)
Site of onset			
Limb			
Upper	16 (29.1%)	5 (9.1%)	21 (38.2%)
Lower	13 (23.6%)	5 (9.1%)	18 (32.7%)
Lower + Upper	1 (1.8%)	0	1 (1.8%)
Bulbar	14 (25.5%)	0	14 (25.5%)
Bulbar + Limb	1 (1.8%)	0	1 (1.8%)
Frontotemporal demans	4 (7.3%)	2 (3.6%)	6 (10.9%)
Treatment			
Riluzole	45 (81.8%)	10 (18.2%)	55 (100%)
Edaravone	2 (3.6%)	1 (1.8%)	3 (5.4%)
Diaphragm pacing system	2 (3.6%)	0	2 (3.6%)
Survival rate			
Alive	25 (45.5%)	1 (1.8%)	26 (47.3%)
Exitus	20 (36.4)	9 (16.3%)	29 (52.7%)

Table 2 Detailed clinical features of ALS patients with mutations

	Gender	AO	SO	Frontotemporal dementia	Mutation	Zygosity	Type
1	M	61	LL	NO	*C9orf72* expansion	het	fALS
2	F	52	UL	NO	*C9orf72* expansion	het	fALS
3	F	59	UL	NO	*C9orf72* expansion	het	fALS
4	M	57	UL	NO	*C9orf72* expansion	het	fALS
5	F	53	UL + LL	NO	*C9orf72* expansion	het	sALS
6	F	52	Bulbar	NO	*C9orf72* expansion	het	sALS
7	M	48	UL	NO	*SOD1* NM_000454.4 c.260A > G p.Asn87Ser	het	sALS
8	F	60	LL	YES	*VCP* NM_007126 c.572G > C p.Arg191Pro	het	fALS
9	F	40	LL	NO	*SH3TC2* NM_0024557.3 c.1568 T > C p.M523T	het	fALS
10	M	56	UL	NO	*TBK1* NM_013254.4 c.1928_1930delAAG; p.Glu643del	hom	fALS
11	F	17	LL	NO	*SPG11* NM_001160227 c.1966-1967del AA p.Lys656Valfs*11	hom	fALS

AO age of onset, *SO* site of onset, *M* male; *F* female, *LL* lower limb, *UL* upper limb, *het* heterozoygous, *hom* homozygous

described, which exhibits dominant inheritance characteristics and is accompanied by dementia symptoms (Fig. 1).

A heterozygous mutation in the *SH3TC2* gene (c.1568 T > C p.Met523Thr, NM_0024577.4) was present in a fALS case. The patient presented with lower limb-onset

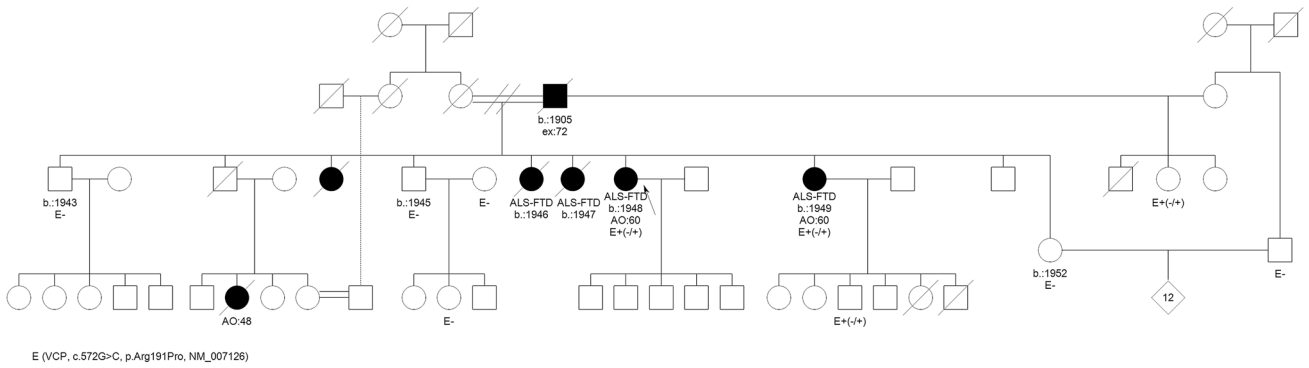

Fig. 1 Pedigree of familial ALS with VCP mutation (c.572G > C p.Arg191Pro, NM_007126). The index patient is shown by the arrow. *Black* ALS patient, *white* unaffected

disease at 46 years of age. An evaluation of the proband's 52-year-old brother and his 50-year-old sister showed a similar pattern of ALS, with the same heterozygous mutation in the *SH3TC2* gene.

A novel homozygous *SPG11* frameshift mutation (c.1966_1967delAA, p.Lys656Valfs*11, NM_025137) was detected in two siblings (one male and one female) with juvenile-onset.

Finally, a rare homozygous mutation in *TBK1* (c.1928_1930delAAG; p.Glu643del, NM_013254.4) was identified in a fALS case with FTD. The mean age at symptom (weakness of upper extremity) onset was 56. Table 2 summarizes the clinical and genetic data of patients whose diagnosis was confirmed by genetic analysis. Pathogenic variants were not detected in the 25 sALS patients subjected to WGS in the following genes: *ALS2, ANG, C19ORF12, CCNF, CHCHD10, CHMP2B, CHRNA3, CHRNA4, CHRNB4, CREST, DAO, DCTN1, ELP3, ERBB4, EWSR1, FIG4, FUS, hnRNPA1, hnRNPA2B1, MATR3, NEFH, NEK1, OPTN, PFN1, PNPLA6, PON1, PON3, PRPH, SETX, SIGMAR1, SOD1, SPG11, SQSTM1, TAF15, TARDBP, TBK1, TUBA4A, UBQLN2, and VAPB.*

Discussion

The physiopathological basis of ALS is selective degeneration of motor neurons with a progressive course. The diagnosis of the disease is very often not straightforward and several other diseases have to be ruled out before a firm diagnosis can be ascertained. Thus, the short life span after the establishment of a diagnosis, the absence of a specific treatment for the disease, and the fast clinical progression render molecular genetic investigation of the disease an important issue. Although a description of the differential diagnosis of ALS is clinically not difficult, a variety of underlying pathophysiological processes lead to the premise that ALS pathophysiology is complex with numerous assumptions made so far [30].

The mean age of onset of ALS varies from 50 to 65 years, commonly ranging between 47 and 52 years for fALS [31, 32]. In our study, the mean age at onset for fALS was 49.9 (range: 17–77) years. A study reported that after 80 years of age, the incidence of ALS rapidly decreases, yet, we report two (3.6%) sALS patients whose ages of onset were 82 and 83 [32].

In accordance with the fact that male gender is an established risk factor for ALS, higher incidence of the disease was seen in male patients compared to women (58.2%) also in this cohort [33, 34]. Worldwide, only 5–10% of ALS cases have a family history and are considered as fALS [8]. In our study, fALS cases were higher in incidence compared to the literature (18.2%, 10/55), which may be due to the high rates of consanguineous marriages in Turkey.

Clinical findings of ALS are seen as various combinations of symptoms due to upper and/or lower neuronal damage at the bulbar region and/or limbs. Progressive muscle weakness and atrophy, speech difficulty, difficulty in swallowing and breathing, and fasciculations are signs of lower motor neuron involvement, and spasticity and hyperreflexity are the primary symptoms of upper motor neuron damage. In the later stages, secondary symptoms such as pain, posture disorders, and loss of mobility that all lower the quality of life of patients may be added [19, 35]. The disease onset site observed in the present cohort, as 25.5% bulbar-onset and 72.7% limb-onset, reflects previous studies [36, 37]. Bulbar-onset disease was not seen among our fALS patients. Muscle atrophy was present in all subjects and the distribution of the atrophy was wide in four patients. Progressive weakness and atrophy of upper limbs and absence of bulbar signs are characteristics of the motor neuron man-in-barrel syndrome [38]. A few cases in whom there was respiratory insufficiency, truncal weakness or dementia, might suggest this is random [37]. A patient with bulbar-onset had weakness of

neck flexor muscles as a rare symptom of ALS. Bulbar-onset fALS is rare [39]. In our study, all bulbar-onset patients had sALS.

Our study revealed causative variants in eleven patients (20%): The genes carrying these variants were *C9orf72* (10.9%), *SOD1* (1.8%), *VCP* (1.8%), *SPG11* (1.8%), *SH3TC2* (1.8%), and *TBK1* (1.8%). Since our cohort covers only the city of Sakarya, our numbers are too small to calculate reliable frequencies; however,, *C9orf72* expansion is by far the most abundant ALS cause also in the current Turkish cohort, supporting the findings of a larger epidemiological study on ALS in Turkey with a genetic profile ranking of *C9orf72* (18.3%), *SOD1* (12.2%), *FUS* (5%), *TARDBP* (3.7%), and *UBQLN2* (2.4%) in fALS [35, 40].

The north to south decrease in the frequency of *C9orf72* expansion across Europe [27] explains the relatively low percentage of *C9orf72* in our cohort and in Turkey at large, although it is the leading gene in the country. In our study, only one patient with a C9orf72 expansion had bulbar-onset. The difference of our overall results as compared to the epidemiological data in Turkey may be explained by several factors, including an intense influx of internal migration to Sakarya region, the presence of multi-ethnicity in this relatively small area, a rapid increase of annual resident population, and the relative rarity of consanguineous marriages.

SOD1-based ALS, which represents 20% of fALS and 5% of sALS, is observed in only one case in our cohort [26]. The heterozygous SOD1-p.Asn87Ser variation detected in our sALS patient with an age of symptom onset of 48 was previously reported in another patient with an earlier age of onset of 37 [41]. The two most common *SOD1* variants causing ALS in Turkey are reported to be the common Balkan variant, SOD1-p.Leu145Phe, and the homozygous-p. Asp91Ala variant [35]. The absence of these two variants in our cohort is not surprising, since Sakarya is not a region that commonly receives migration from the Balkans. Furthermore, consanguinity in the cohort under study was rare. This observation might partly explain the decreased percentage of *SOD1*-based ALS in our study. The low number of common fALS mutations is the result of low fALS cases in this study.

In this study, we were able to identify causative variants in all four cases that were analyzed by WES. Two of the cases solved had strong family histories and the other two were offspring to consanguineous parents. The heterozygous VCP variant (p.Arg191Pro) identified in a female fALS patient, also detected in additional five affected family members, caused hallucinations and dementia in addition to ALS symptoms. Mutations in *SPG11* are most common cause of hereditary spastic paraplegia [42]. But these mutations can cause rare forms of juvenile-onset ALS as well [43]. In our study, the novel homozygous SPG11 frameshift mutation (c.1966_1967delAA, p.Lys656Valfs*11) was detected in two siblings (one male and one female) with juvenile-onset. Mutations in *TBK1* are cause of impaired autophagy and contribute to the accumulation of protein aggregates and ALS pathology [44]. A study reported that *TBK1* mutations occurred more frequently in patients with FTD-ALS comorbidity (10.8%) than in patients with ALS alone (0.5%) [45–47]. In accordance with this observation, our fALS case with the homozygous *TBK1* (p.Glu643del) variant showed FTD symptoms accompanying ALS. The patient's father and two paternal uncles were reported to have pure FTD and his two sisters died with ALS-FTD. Finally, the heterozygous p.Met523Thr variant in the *SH3TC2* gene was detected in a female ALS patient and two affected siblings. In this extended family in which several affected members are described, segregation analysis is ongoing and it cannot be claimed that the above variant in the *SH3TC2* gene is the only gene variant responsible of the phenotype. Autosomal dominant mutations in the *SH3TC2* gene have been previously associated with mononeuropathy of the median nerve [48].

Genetic variants identified in this small cohort once more point to the genetic heterogeneity well-established in ALS. Further research is pending in cases in whom the underlying genetic defect could not be unraveled yet.

Riluzole and Edaravone are the only two drugs approved by the FDA for ALS, a disease with limited treatment options and no effective therapies [49]. Thus, improving the quality of life of patients with palliative therapies is of utmost importance. In this study, we started riluzole and proper palliative therapies in patients with established diagnoses of ALS. Two patients had also a diaphragm pacing system. During the follow-up period, twenty-three patients died.

Epidemiological studies on ALS may help to understand the effects of environmental factors on disease development and the status of genetic and geographical factors in ALS etiology. Thus, we hope that the clinical and genetic findings presented here contribute to the literature.

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Author contributions ZÖA, DK, CT, FA, ANB provided author's contributions concepts. DK, ZÖA, CT, FA, ANB involved in design. ZÖA, DK, BDG, CT, FA, ANB contributed materials. ZÖA, DK, BDG, CT, FA, ANB collected the data. ZÖA, CT, DK, ANB performed literature search. ZÖA, CT, DK, ANB wrote the manuscript. ANB, ZÖA, CT, DK involved in critical reviews.

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Data availability Data are avaliable.

Compliance with ethical standards

Conflict of interest No conflict of interest was declared by the authors.

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