EJCRIM
European Journal
of Case Reports
in Internal Medicine

A VERY RARE SETX GENE VARIANT (C.2750T>C) IN A 72-YEAR-OLD MAN WITH AMYOTROPHIC LATERAL SCLEROSIS AND AN UNREMARKABLE FAMILY HISTORY. SHOULD GENETIC TESTING BE ROUTINELY PERFORMED IN ALL PATIENTS?

Andreas Posa[1], Malte Kornhuber[2,3]

[1] Department of Radiology and Neuroradiology, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[2] Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[3] Department of Neurology, Helios Hospital Sangerhausen, Sangerhausen, Germany

Corresponding author's e-mail: andreas.posa@medizin.uni-halle.de

Received: 18/07/2025
Accepted: 28/07/2025
Published: 23/09/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: During his hospitalisation, the adult patient gave his written informed consent on the hospital's internal data protection forms to the use of his patient-related data in anonymised form for scientific publication.

How to cite this article: Posa A, Kornhuber M. A very rare SETX gene variant (c.2750T>C) in a 72-year-old man with amyotrophic lateral sclerosis and an unremarkable family history. Should genetic testing be routinely performed in all patients? *EJCRIM* 2025;**12**:doi:10.12890/2025_005706

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative multisystem disease with loss of spinal, bulbar and cortical upper and lower motor neurons resulting in progressive and generalised paralysis. Unfortunately, many aspects of this disease remain unclear. In the age of next generation sequencing, numerous gene variants have been discovered that are associated with ALS. In this article, a 72-year-old male underwent a medical history interview, clinical neurological examinations, neuropsychological tests, electrophysiological examinations (electromyography, electroneurography, somatosensory evoked potentials), computed tomography scan of the head and the cervical spine, blood and cerebrospinal fluid tests and a genetic analysis. The results of these examinations provided the definitive diagnosis of ALS. Whole-exome sequencing revealed the very rare genetic finding of the *SETX* Class-4 variant c.2750T>C (p.Met917Thr). The case presented here discusses the role of the *SETX* gene as a possible pathogenetic variant of adult-onset ALS. It demonstrates the relevance of genetic screening for gene variants of ALS in routine diagnostics. The precise classification of disease-related gene variants is of great relevance for clinical practice.

KEYWORDS

Amyotrophic lateral sclerosis, motor neurone disease, neurodegenerative multisystem disease, *SETX* gene, senataxin protein

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative multisystem disease with loss of spinal, bulbar and cortical upper and lower motor neurons resulting in progressive and generalised paralysis.
- The case presented here describes a very rare variant in the *SETX* gene (heterozygous Class-4 variant c.2750T>C, p.Met917Thr) in an adult man with sporadic rapidly progressive ALS, with an unremarkable family history.
- This case demonstrates the relevance of genetic screening for gene variants of ALS in routine diagnostics, both in sporadic and familial cases. This may add to the accuracy of diagnosis and may improve genetic counselling for rare diseases.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative multisystem disease with loss of spinal, bulbar and cortical upper and lower motor neurons resulting in progressive and generalised paralysis[1]. The diagnosis is based on clinical signs, typical electromyography findings, and genetic confirmation in a minority of cases. Most cases (~90%) of adult ALS are sporadic (sALS), while ~10% of the patients have a family history of ALS (fALS)[1]. Given the numerous and diverse genetic mechanisms in ALS, it is noteworthy that a substantial percentage of individuals with a positive family history remain without identification of a genetic defect. This suggests relevant heterogeneity in the spectrum of this disease. The case presented here describes a very rare variant in the *SETX* gene in an adult man with ALS, with an unremarkable family history.

CASE DESCRIPTION

We report a 72-year-old male diagnosed with ALS, with a heterozygous Class-4 variant c.2750T>C (p.Met917Thr) in the *SETX* gene (whole-exome sequencing; see *Appendix*). The first symptoms appeared at the age of 70, with muscle cramps in both legs on exertion. About half a year later, the strength in both arms decreased. The right arm was slightly more affected than the left arm. Within a few months, this reduction in strength spread rightward and distally to the whole body (arms, legs, shoulder-neck area, camptocormia, head extensor weakness). In addition, bulbar complaints (dysphagia, dysarthria), marked fasciculations (arms, legs) and hyperreflexia (biceps tendon reflex, pectoral tendon reflex, adductor muscle reflex, patellar tendon reflex) were evident. Since then, a marked progression of symptoms was noted, with significant muscle loss (weight loss 17 kg in 1.5 years). Sensation testing was unremarkable. Family history was unremarkable.

The findings of the clinical examination correspond to definitive ALS according to the revised El Escorial criteria, with impairment of the upper and lower motor neurons in at least three body regions. Electromyographic diagnosis indicated acute degeneration of the second motoneuron. Serum-levels of neurofilament light chain (NfL) were markedly increased (133 pg/ml; reference <62 pg/ml). Cerebrospinal fluid diagnostic was normal, as were electroneurography, somatosensory evoked potentials, electrocardiography and computed tomography of the head and the cervical spine (non-magnetic resonance imaging-conditional pacemaker implanted). Special laboratory analyses were unremarkable for paraneoplastic and anti-neuronal antibodies. The neuropsychological tests were normal.

Due to the aforementioned clinical, electrodiagnostic and serological findings, definitive ALS was diagnosed 1.5 years after symptom onset at the age of 71. Since ALS is currently an incurable neurodegenerative disease, causal therapy was not possible. The patient died after a rapid and unstoppable malignant progression at the age of 73.

DISCUSSION

The *SETX* gene encodes the senataxin protein (approximately 2,677 amino acids; ~306 kDa), which has deoxyribonucleic acid/ribonucleic acid (DNA/RNA) helicase activity and is considered to play an important role in DNA double-strand repair and RNA splicing mechanisms[2]. Senataxin is involved in DNA repair, replication, recombination, transcription, RNA processing, transcript stability, translation initiation and autophagy regulation[2]. In addition, senataxin appears to be important for the myelin of central and peripheral motor nerves, the neuronal soma and axons[3].

The *SETX* variant presented here was previously classified as a variant of unclear significance in various genetic databases (ClinVar, LOVD). Various bioinformatics programmes classify this gene variant as benign (PolyPhen-2 score 0.011, sensitivity 0.96, specificity 0.78), as tolerable (SIFT) or as a polymorphism (MutationTaster), with a CADD score of 5.835, indicating that this variant is probably benign and may not be a causative factor for ALS. In contrast, the gene variant presented here was considered as probably pathogenic in two very rare cases of adult-onset ALS[5].

Heterozygous missense variants at other locations in the *SETX* gene have been described to cause a rare (0.3-2%) form of autosomal dominant juvenile ALS (*ALS4*), possibly mediated via interaction with the zinc finger protein ZPR1[3,4,6]. These patients show an earlier onset (<6 years) but tend to have a slower disease progression with a longer disease duration, as well as atypical features (pes cavus, contractures of the Achilles tendon, hammer toes, sensory impairment)[6,7]. To date, various missense pathogenic *SETX* gene variants have been described in *ALS4*[7]. The exact mechanism of *SETX*-dependent motor neuron toxicity is not yet well understood. The *SETX* variant reported here has

been associated with a late-onset and rapidly progressive ALS phenotype[5].

The absence of a relevant family history, as in our case, does not exclude a genetic cause of ALS, especially in small families[5]. A population based systematic assessment of ALS genetics showed that *SETX* pathogenetic variants are present in about 1% of patients, mostly without a family history of ALS[8]. In a few cases, mutations in the *SETX* gene have been detected in asymptomatic carriers from an ALS family[3]. Therefore, incomplete or lower disease penetrance should be considered. Due to the relatively high frequency of heterozygous *SETX* variants in both patients and control subjects, it is debatable whether this gene is responsible for a substantial proportion of genetic ALS or whether it should rather be considered as a genetic susceptibility factor[5]. In this regard, alterations in the *SETX* gene may not necessarily indicate ALS[9]. In addition, alterations in the *SETX* gene also occur in other neurological diseases (ataxia, oculomotor apraxia, neuropathy, spinal muscular atrophy).

This case demonstrates the relevance of genetic screening for gene variants of ALS in routine diagnostics, both in sporadic and familial cases, and thus also in adult patients without a family history of ALS. This may add to the accuracy of diagnosis and may improve genetic counselling for rare diseases.

APPENDIX

Unremarkable genetic diagnosis: *AARS1*, *ABCA1*, *ABCD1*, *ABHD12*, *ABHD5*, *ACADM*, *ACADS*, *ACADVL*, *ACTA1*, *ACTC1*, *ACTN2*, *AFG3L2*, *AGK*, *AGL*, *AGRN*, *AIFM1*, *AIMP1*, *ALDH18A1*, *ALDOA*, *ALG13*, *ALG14*, *ALG2*, *ALS2*, *AMPD2*, *ANG*, *ANK2*, *ANKRD1*, *AN05*, *AP4B1*, *AP4E1*, *AP4M1*, *AP4S1*, *APP*, *APTX*, *ARHGEF10*, *ARL61P1*, *ASAH1*, *ATL1*, *ATL3*, *ATP2A1*, *ATP7A*, *ATXN2*, *B3GALNT2*, *B4GALNT1*, *B4GAT1*, *BAG3*, *BICD2*, *BINI*, *BSCL2*, *C9ORF72*, *CACNA1A*, *CACNA1S*, *CACNB4*, *CAPN3*, *CAV3*, *CAVIN1*, *CCDC78*, *CCT5*, *CFL2*, *CHAT*, *CHCHD10*, *CHKB*, *CHMP2B*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *CHRNG*, *CHST14*, *CLCN1*, *CNTN1*, *COL12A1*, *COL4A1*, *COL4A2*, *COL5A1*, *COL5A2*, *COL6A1*, *COL6A2*, *COL6A3*, *COLQ*, *COQ8A*, *COX10*, *COX15*, *COX6A1*, *CPT1C*, *CPT2*, *CRPPA*, *CRYAB*, *CSRP3*, *CTDP1*, *CYP27A1*, *CYP2U1*, *CYP7B1*, *DAG1*, *DAO*, *DARS2*, *DCAF8*, *DCTN1*, *DDHD1*, *DDHD2*, *DES*, *DGUOK*, *DHTKD1*, *DMD*, *DNA2*, *DNAJB2*, *DNAJB6*, *DNM2*, *DNMT1*, *DOK7*, *DOLK*, *DPAGT1*, *DPM1*, *DPM2*, *DPM3*, *DYNC1H1*, *DYSF*, *EGR2*, *ELP1*, *EMD*, *EN03*, *ENTPD1*, *ERBB4*, *ERL1N1*, *ERL1N2*, *ETFA*, *ETFB*, *ETFDH*, *FA2H*, *FAM3B*, *FAM126A*, *FBLN5*, *FBX038*, *FGD4*, *FHL1*, *FIG4*, *FKBP14*, *FKRP*, *FKTN*, *FLNC*, *FUS*, *G6PC1*, *GAA*, *GAD1*, *GALC*, *GAN*, *GARS1*, *GBA2*, *GBE1*, *GCH1*, *GDAP1*, *GFAP*, *GFPT1*, *GJB1*, *GJB3*, *GJQ*, *GLB1*, *GMPPB*, *GNB4*, *GNE*, *GRID2*, *GRN*, *GYS1*, *HADH*, *HADHA*, *HADHB*, *HARS1*, *HEXA*, *HINT1*, *HK1*, *HMBF*, *HNRNPA1*, *HNRNPDL*, *HOXD10*, *HSPB1*, *HSPB3*, *HSPB8*, *HSPD1*, *HSPG2*, *IBA57*, *IGHMBP2*, *INF2*, *ISCU*, *ITGA7*, *JPH2*, *KARS1*, *KBTBD13*, *KCNA1*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *KIF1A*, *KIF1B*, *KIF1C*, *KIF21A*, *KIF5A*, *KLHL40*, *KLHL41*, *KLHL9*, *LICAM*, *LAMA2*, *LAMB2*, *LAMP2*, *LARGE1*, *LDB3*, *LDHA*, *LITAF*, *LMNA*, *LMOD3*, *LPIN1*, *LRP4*, *LRSAM1*, *MAG*, *MAPT*, *MARS1*, *MARS2*, *MATR3*, *MED25*, *MEGFIO*, *MFN2*, *MGME1*, *MPV17*, *MPZ*, *MSTN*, *MTM1*, *MTMR14*, *MTMR2*, *MTO1*, *MTPAP*, *MTRFR*, *MUSK*, *MYBPC1*, *MYBPC3*, *MYF6*, *MYH14*, *MYH2*, *MYH3*, *MYH6*, *MYH7*, *MYL2*, *MYL3*, *MYOT*, *MYOZ2*, *MYPN*, *NDRG1*, *NDUFAF5*, *NEB*, *NEFH*, *NEFL*, *NEK1*, *NEXN*, *NGF*, *NIPA1*, *NT5C2*, *NTRK1*, *OPAI*, *OPA3*, *OPTN*, *PABPN1*, *PANK2*, *PARK7*, *PDK3*, *PDYN*, *PEX12*, *PFKM*, *PFN1*, *PGAM2*, *PGK1*, *PGM1*, *PHKA1*, *PHKA2*, *PHKB*, *PHKG2*, *PHOX2A*, *PLA2G6*, *PLEC*, *PLEKHG5*, *PLN*, *PIP1*, *PMP22*, *PNPLA2*, *PNPLA6*, *POLG*, *POLG2*, *POMGNT1*, *POMGNT2*, *POMK*, *POMT1*, *POMT2*, *PON1*, *PON2*, *PON3*, *PPARGC1A*, *PRKAG2*, *PRPH*, *PRPS1*, *PRX*, *PSEN1*, *PSEN2*, *PYGM*, *RAB7A*, *RAPSN*, *RBCK1*, *RBM20*, *REEP1*, *REEP2*, *RETREG1*, *RRM2B*, *RTN2*, *RXYLT1*, *RYR1*, *SACS*, *SBF1*, *SBF2*, *SCN2A*, *scN4A*, *SCN5A*, *SCN9A*, *SC02*, *SELENON*, *SEP-TIN9*, *SGCA*, *SGCD*, *SGCG*, *SH3TC2*, *SIGMAR1*, *SilI*, *SLC12A6*, *SLC16A2*, *SLC1A3*, *SLC22A5*, *SLC25A20*, *SLC25A3*, *SLC25A4*, *SLC2A1*, *SLC33A1*, *SLC37A4*, *SLC52A2*, *SLC52A3*, *SLC5A7*, *SMCHD1*, *SNAP25*, *SNTA1*, *SOD1*, *SOX10*, *SPART*, *SPAST*, *SPEG*, *SPG2*, *SPG21*, *SPG7*, *SPR*, *SPTLC1*, *SPTLC2*, *SQSTM1*, *STIM1*, *SUCLA2*, *SUCLG1*, *SURF1*, *SYNE1*, *SYNE2*, *SYT2*, *TARDBP*, *TBK1*, *TCAP*, *TDP1*, *TECPR2*, *TFG*, *TH*, *TIA1*, *TK2*, *TMEM43*, *TMPO*, *TNNC1*, *TNN12*, *TNN13*, *TNNT1*, *TNNT2*, *TNNT3*, *TNP03*, *TPM1*, *TPM2*, *TPM3*, *TRAPPC2*, *TREM2*, *TRIM2*, *TRIM32*, *TRPM7*, *TRPV4*, *TTN*, *TTR*, *TUBA4A*, *TUBB3*, *TUBB4A*, *TWNK*, *TYMP*, *UBA1*, *UBQLN2*, *VAMP1*, *VAPB*, *VCL*, *vcp*, *VMA21*, *VPS37A*, *VRK1*, *WASHC5*, *WNK1*, *YARS1*, *YARS2*, *ZFYVE26*, *ZFYVE27*.

REFERENCES

1. González-Sánchez M, Ramírez-Expósito MJ, Martínez-Martos JM. Pathophysiology, clinical heterogeneity, and therapeutic advances in amyotrophic lateral sclerosis: A comprehensive review of molecular mechanisms, diagnostic challenges, and multidisciplinary management strategies. *Life* 2025;**15**:647. doi: 10.3390/life15040647
2. Bennett CL, La Spada AR. SUMOylated Senataxin functions in genome stability, RNA degradation, and stress granule disassembly, and is linked with inherited ataxia and motor neuron disease. *Mol Genet Genomic Med* 2021;**9**:e1745. doi: 10.1002/mgg3.1745
3. Lei L, Chen H, Lu Y, Zhu W, Ouyang Y, Duo J, et al. Unusual electrophysiological findings in a Chinese ALS 4 family with SETX-L389S mutation: a three-year follow-up. *J Neurol* 2021;**268**:1050-1058. doi: 10.1007/s00415-020-10246-2
4. Kannan A, Cuartas J, Gangwani P, Branzei D, Gangwani L. Mutation in senataxin alters the mechanism of R-loop resolution in amyotrophic lateral sclerosis 4. *Brain* 2022;**145**:3072-3094. doi: 10.1093/brain/awab464
5. Pensato V, Magri S, Dalla Bella E, Tannorella P, Bersano E, Sorarù G, et al. Sorting rare ALS genetic variants by targeted re-sequencing panel in Italian patients: OPTN, VCP, and SQSTM1 variants account for 3% of rare genetic forms. *J Clin Med* 2020;**9**:412. doi: 10.3390/jcm9020412
6. Picher-Martel V, Brunet F, Dupré N, Chrestian N. The occurrence of FUS mutations in pediatric amyotrophic lateral sclerosis: a case report and review of the literature. *J Child Neurol* 2020;**35**:556-562. doi: 10.1177/0883073820915099
7. Hadjinicolaou A, Ngo KJ, Conway DY, Provias JP, Baker SK, Brady LI, et al. De novo pathogenic variant in SETX causes a rapidly progressive neurodegenerative disorder of early childhood-onset with severe axonal polyneuropathy. *Acta Neuropathol Commun* 2021;**9**:194. doi: 10.1186/s40478-021-01277-5
8. Grassano M, Calvo A, Moglia C, Sbaiz L, Brunetti M, Barberis M, et al. Systematic evaluation of genetic mutations in ALS: a population-based study. *J Neurol Neurosurg Psychiatry* 2022;**93**:1190-1193. doi: 10.1136/jnnp-2022-328931
9. Finsterer J, Stöllberger C, Keller H, Laccone F. Variants in HNRNPDL and SETX not necessarily indicate familial amyotrophic lateral sclerosis or limb girdle muscular dystrophy 1G in acute muscular respiratory failure. *J Neurosci Rural Pract* 2020;**11**:353-354. doi: 10.1055/s-0040-1709375