CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

TARDBP Mutations in Facial-Onset Sensory and Motor Neuronopathy

Vincent Picher-Martel, MD, PhD, Suma Babu, MBBS, MPH, and Anthony A. Amato, MD

Neurol Genet 2024;10:e200160. doi:10.1212/NXG.0000000000200160

Correspondence
Dr. Picher-Martel
vmartel@bwh.harvard.edu

Abstract

Objectives

Facial-onset sensory and motor neuronopathy (FOSMN) is a rare neuromuscular disorder characterized by progressive facial sensory impairment followed by motor dysfunction in a rostro-caudal distribution. FOSMN is clinically and pathologically associated with amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD). In contrast to ALS/FTD, the genetic profile of patients with FOSMN and the role of genetic testing are poorly defined.

Methods

A 66-year-old woman was evaluated in our neuromuscular clinic for progressive facial pain, dysphagia, and dysarthria. Her diagnostic evaluation included brain and cervical MRI, nerve conduction studies and EMG, and an ALS/FTD next-generation sequencing panel.

Results

The patient was diagnosed with FOSMN, and we identified a N390D variant in transactive response DNA-binding protein (TDP-43/*TARDBP*). This variant has never been reported in FOSMN but was previously reported in 2 cases of ALS, and a N390S variant was also previously reported in FOSMN. A review of the literature revealed that *TARDBP* mutations are over-represented in patients with FOSMN compared with patients with ALS/FTD. By contrast, other common familial forms of ALS, including *C9ORF72* or *SOD1*, are respectively absent or rare in FOSMN.

Discussion

FOSMN is pathologically and genetically associated with TDP-43. Therefore, ALS genetic testing that includes specifically *TARDBP* should be considered in patients with FOSMN.

Introduction

Facial onset sensory and motor neuronopathy (FOSMN) is a rare neuromuscular disorder characterized by progressive facial paresthesia with subsequent development of sensory and motor manifestations in a rostro-caudal distribution.[1] Although few reports have suggested the presence of a modest response to immunotherapy,[2,3] more recent evidence is supportive of a neurodegenerative process with TAR DNA-binding protein 43 (TDP-43/*TARDBP*) inclusions in sensory and motor brainstem nuclei.[4] In rare instances, FOSMN can also be associated with cognitive or personality changes with frontal cortex TDP-43 accumulation,[5] suggesting that FOSMN may be part of the amyotrophic lateral sclerosis and fronto-temporal dementia (ALS/FTD) spectrum. Although some cases were found to carry genetic variants, the genetic landscape of the disease needs to be clarified.[1]

From the Department of Neurology (V.P.-M.), Massachusetts General Hospital/Harvard Medical School; Department of Neurology (V.P.-M.), MassGeneral Institute for Neurodegenerative Diseases (MIND); Department of Neurology (S.B.), Massachusetts General Hospital; Department of Neurology (A.A.A.), Brigham Women's Hospital, Harvard Medical School, Boston, MA.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing charge was funded by the authors.

Clinical Description

A 66-year-old woman presented for evaluation of facial pain, dysphagia, and dysarthria. About 2 years ago, she developed bilateral burning sensation in her lips and teeth. It slowly progressed over months to affect her palate, tongue, and cheeks, and she eventually developed numbness in her cheeks, around the eyes, forehead, and scalp. One year later, she developed dysarthria and dysphagia and lost about 45 pounds. She described mild eye and mouth dryness but denied any sensory or motor symptoms in the limbs.

Neurologic examination revealed moderate flaccid dysarthria without aphasia. There was mild-to-moderate eye closure and facial weakness, tongue atrophy with numerous tongue, and chin fasciculations. Her corneal and nasociliary reflexes were bilaterally absent. She had normal pinprick and light touch sensation in the face. Motor examination revealed a significant neck flexion weakness (MRC 3-/5), mild bilateral distal hand weakness in the finger extensors (MRC 4+/5), and mild proximal lower extremities weakness (hip flexors MRC 4+/5; hip abductors MRC 4+/5). There was no muscle atrophy or fasciculations in the limbs. Deep tendon reflexes were normal. The remaining neurologic examination was otherwise unrevealing, and her Edinburgh Cognitive and Behavioral ALS Screen total score was 126/136.

Cervical spine and brain MRI were normal. Nerve conduction studies and EMG, 2 years after her initial symptoms, showed normal median, ulnar, radial, and sural sensory nerve action potentials, as well as normal median, ulnar, peroneal, and tibial compound muscle action potentials. However, bilateral blink reflexes were absent. There were fibrillations potentials and positive sharp waves in the right sternocleidomastoid, biceps, and medial chief of the gastrocnemius muscle with fasciculations potentials in the right sternocleidomastoid and deltoid and complex repetitive discharges in the right deltoid. There was chronic denervation and reinnervation in the tongue, right sternocleidomastoid, and trapezius muscles. Right triceps, pronator teres, first dorsal interosseous, vastus medialis, and tibialis anterior were normal. A diagnosis of clinically probable FOSMN was made.

Genetic Analysis and the Role of *TARDBP* Mutation in FOSMN

A next-generation sequencing panel of 22 confirmed ALS genes from Invitae (May 8 2023, San Francisco, CA) was performed and revealed a heterozygous c.1168A>G (p.Asn390Asp; N390D) variant in *TARDPB* gene. The N390D variant was previously described in at least 2 cases of definite ALS,[6,7] and functional studies revealed that this variant disrupt protein function leads to TDP-43 aggregation and causes toxicity in vitro[8] and in vivo.[9] The PolyPhen-2 algorithm (Harvard University) predicts that the variant is probably damaging (score 0.989). Therefore, this variant is classified as pathogenic by ClinVar (NIH) and most likely pathogenic in this case.

On review of literature, we found a total of 107 patients with FOSMN in 30 different articles before July 2023. We extracted the total number of patients, the presence of family history of FOSMN or ALS, genetic analysis, the patients tested for *TARDBP*, *SOD1*, *C9ORF72*, or other ALS genes and all reported gene variants. Including our patient, a total of 8 patients were reported to have a genetic variant. One patient was reported to have a mutation in the *PAPBN1* gene associated with oculopharyngeal muscular dystrophy and was not included in the analysis. Therefore, including our case, a total of 7 of 107 (6.5%) FOSMN cases carried a variant, and 6 patients (5.6%) had a family history of ALS/FTD (2/6 with identified genes), but none had a family history of FOSMN. A variant was found in 7 of 57 (12.3%) patients who have been tested for any genetic abnormality (ALS genes/panel, Kennedy disease, spinocerebellar ataxia panel, whole-exome sequencing). *TARDBP* variant has been described in 3 other cases and appears to be the most frequent gene involved in FOSMN pathogenesis. Indeed, a *TARDPB* variant was found in 4 of 26 (15.4%) patients tested for variants in this gene. Conversely, no *C9ORF72* repeat expansion was found in 36 tested patients, and only one *SOD1* variant was found in 35 tested patients (2.9%).[10] The 3 other genetic variants were described in *SQSTM1*, *VCP*, and *CHCHD10*[11,12] (Table). All FOSMN variants described in *TARDBP* gene are in the C-terminal glycine-rich domain of the protein (Figure). A dual N390S (c.1169A>G) *TARDBP* variant with a P392L (c.1175C>T) *SQSTM1* variant was previously described in a 77-year-old male patient with FOSMN.[12] Of note, his 2 healthy siblings carried the *SQSTM1* variant, but not the *TARDBP* variant, suggesting that the latter may be pathogenic or the *SQSTM1* variant has low penetrance.

Discussion

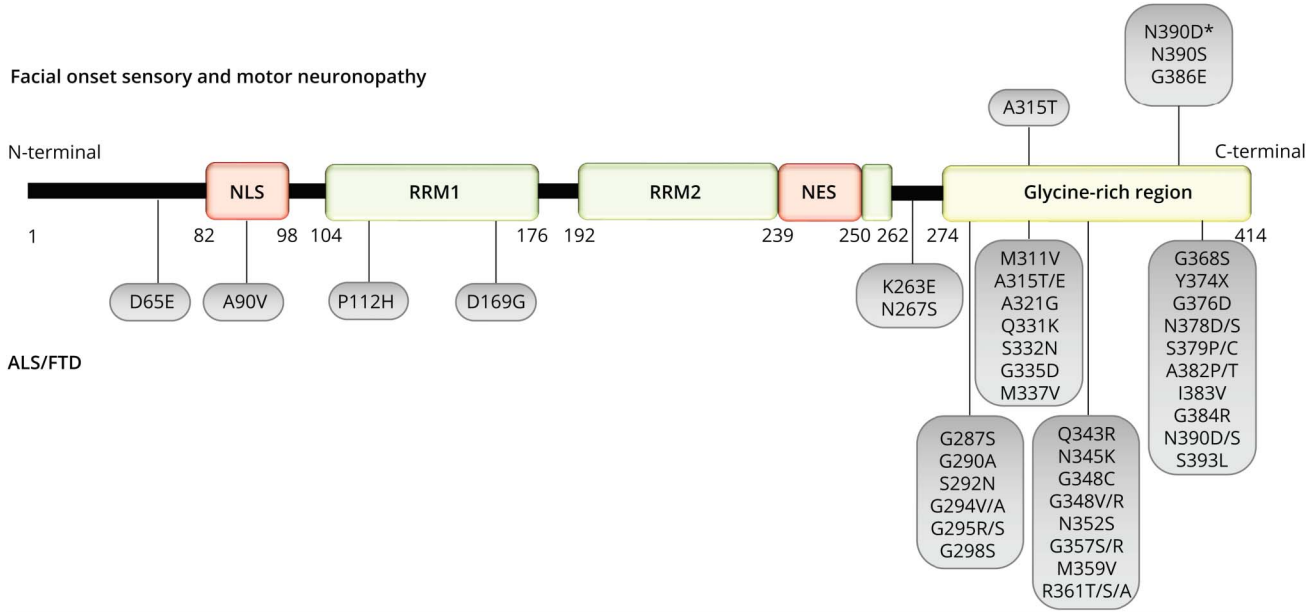
We report a woman with FOSMN carrying a N390D mutation in *TARDBP*. She exhibited all typical findings of the

Table Identified Genetic Variants in FOSMN

Gene	Variant	Protein change	Number of cases	Identified in ALS/FTD	Reference
TARDBP	c.943G>A	A315T	1	Y	[11]
	c.1157G>A	G386E	1	N	[15]
	c.1168A>G	N390D	1	Y	Present study
	c.1169A>G	N390S	1	Y	[12]
CHCHD10	c.100C>T	P34S	1	Y	[11]
SQSTM1	c.1175C>T	P392L	1	Y	[12]
SOD1	c.272A>C	D90A[a]	1	Y	[10]
VCP	c.464G>A	R155H	1	Y	[11]

[a] D90A is also known as D91A.

Figure TDP-43 Domains and FOSMN-Associated Variants



TDP-43 is composed of 2 RRM domains (RRM1 and RRM2), a nuclear localization signal (NLS), a nuclear export signal (NES), and a C-terminal glycine-rich domain. All FOSMN-associated variants and most ALS/FTD variants are localized in the glycine-rich region. *Variant described here.

disease and fulfilled the proposed diagnosis criteria.[13] Although the clinical presentation of FOSMN is well described, this work is of particular interest because it (1) emphasizes the role of TDP-43 in FOSMN, (2) highlights the importance of genetic assessment in FOSMN, and (3) helps provide further insight into the association between the ALS/FTD spectrum and FOSMN.

TDP-43 cytoplasmic mislocalization and aggregation is the pathologic hallmark of ALS, seen in more than 95% of sporadic cases. Although TDP-43 aggregates are found in most ALS/FTD cases, only about 4% of familial ALS and less than 1% of all cases carry a *TARDBP* mutation. This case and our review of the literature suggest that mutations in *TARDBP* may be overrepresented in FOSMN compared with ALS/FTD. A mutation in the gene was found in 3.7% (4/107) of all FOSMN cases, 7.0% (4/57) of cases with any genetic testing, and 15.4% (4/26) of patients specifically tested for mutations in *TARDPB*. By contrast, no repeat expansion was found in *C9ORF72* gene, the most common genetic form of ALS/FTD, and only one *SOD1* variant was found. Although we acknowledge the inherent limitations in compiling case reports and its possible reporting bias, this is suggestive of a different genotypic landscape in FOSMN compared with ALS/FTD.

TDP-43 is implicated in mRNA processing, transport, and translation through the interaction with its RRM1/RRM2 domains. Its C-terminal glycine-rich domain is mostly implicated in protein-protein interaction. Most variants in FOSMN are described within a few amino acids range (G386E, N390S, N390D) in this domain. A mutation in the same protein region (A382P) was also described in a patient with limb-onset sensory and motor neuronopathy.[14] While this may suggest a hot spot for TDP-43 dysfunction in sensory neurons, the same variants and other closely located variants were described in typical ALS (Figure). Therefore, it remains unclear how the same mutations can lead to either a predominant sensory neuronopathy or a pure motor neuronopathy. Functional studies on N390D *TARDBP* variant compared with other ALS variant could provide important insights.

In conclusion, we presented a case of FOSMN with a N390D variant in *TARDBP*. Mutations in *TARDBP* appear to be significantly associated with the risk of developing FOSMN and genetic testing with an ALS/FTD panel should be considered.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* February 15, 2024. Accepted in final form April 19, 2024. Submitted and externally peer reviewed. The handling editor was Editor Stefan M. Pulst, MD, Dr med, FAAN.

Appendix Authors

Name	Location	Contribution
Vincent Picher-Martel, MD, PhD	Department of Neurology, Massachusetts General Hospital/Harvard Medical School; Department of Neurology, MassGeneral Institute for Neurodegenerative Diseases (MIND), Massachusetts General Hospital, Harvard Medical School, Boston	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Suma Babu, MBBS, MPH	Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Drafting/revision of the manuscript for content, including medical writing for content
Anthony A. Amato, MD	Department of Neurology, Brigham Women's Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Hu N, Zhang L, Yang X, Fu H, Cui L, Liu M. Facial onset sensory and motor neuronopathy (FOSMN syndrome): cases series and systematic review. *Neurol Sci.* 2023;44(6):1969-1978. doi:10.1007/s10072-023-06703-1
2. Knopp M, Vaghela NN, Shanmugam SV, Rajabally YA. Facial onset sensory motor neuronopathy: an immunoglobulin-responsive case. *J Clin Neuromuscul Dis.* 2013; 14(4):176-179. doi:10.1097/CND.0b013e31828ee8fe
3. Hokonohara T, Shigeto H, Kawano Y, Ohyagi Y, Uehara M, Kira J. Facial onset sensory and motor neuronopathy (FOSMN) syndrome responding to immunotherapies. *J Neurol Sci.* 2008;275(1-2):157-158. doi:10.1016/j.jns.2008.07.021
4. Sonoda K, Sasaki K, Tateishi T, et al. TAR DNA-binding protein 43 pathology in a case clinically diagnosed with facial-onset sensory and motor neuronopathy syndrome: an autopsied case report and a review of the literature. *J Neurol Sci.* 2013; 332(1-2):148-153. doi:10.1016/j.jns.2013.06.027
5. Rossor AM, Jaunmuktane Z, Rossor MN, Hoti G, Reilly MM. TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN. *Neurology*. 2019;92(9):e951-e956. doi:10.1212/WNL.0000000000007008
6. Kabashi E, Valdmanis PN, Dion P, et al. TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. *Nat Genet.* 2008;40(5):572-574. doi:10.1038/ng.132
7. Ticozzi N, LeClerc AL, van Blitterswijk M, et al. Mutational analysis of TARDBP in neurodegenerative diseases. *Neurobiol Aging.* 2011;32(11):2096-2099. doi:10.1016/j.neurobiolaging.2009.11.018
8. Wu L-S, Cheng W-C, Shen C-KJ. Similar dose-dependence of motor neuron cell death caused by wild type human TDP-43 and mutants with ALS-associated amino acid substitutions. *J Biomed Sci.* 2013;20(1):33. doi:10.1186/1423-0127-20-33
9. Voigt A, Herholz D, Fiesel FC, et al. TDP-43-mediated neuron loss in vivo requires RNA-binding activity. *PLoS One*. 2010;5(8):e12247. doi:10.1371/journal.pone.0012247
10. Dalla Bella E, Rigamonti A, Mantero V, et al. Heterozygous D90A-SOD1 mutation in a patient with facial onset sensory motor neuronopathy (FOSMN) syndrome: a bridge to amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2014;85(9): 1009-1011. doi:10.1136/jnnp-2013-307416
11. Pinto WBVR, Naylor FGM, Chieia MAT, de Souza PVS, Oliveira ASB. New findings in facial-onset sensory and motor neuronopathy (FOSMN) syndrome. *Rev Neurol (Paris)*. 2019;175(4):238-246. doi:10.1016/j.neurol.2018.04.010
12. Vázquez-Costa JF, Pedrola Vidal L, Moreau-Le Lan S, et al. Facial onset sensory and motor neuronopathy: a motor neuron disease with an oligogenic origin? *Amyotroph Lateral Scler Frontotemporal Degener.* 2019;20(3-4):172-175. doi: 10.1080/21678421.2019.1582671
13. Zheng Q, Chu L, Tan L, Zhang H. Facial onset sensory and motor neuronopathy. *Neurol Sci.* 2016;37(12):1905-1909. doi:10.1007/s10072-016-2686-7
14. Camdessanché J-P, Belzil VV, Jousserand G, et al. Sensory and motor neuronopathy in a patient with the A382P TDP-43 mutation. *Orphanet J Rare Dis.* 2011;6:4. doi: 10.1186/1750-1172-6-4
15. Zhang Q, Cao B, Chen Y, et al. Facial onset motor and sensory neuronopathy syndrome with a novel TARDBP mutation. *Neurologist*. 2019;24(1):22-25. doi: 10.1097/NRL.0000000000000201