A Turkish Family with a Familial ALS-positive UBQLN2-S340I Mutation

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Dear Editor,

We observed a family with a new and rarely encountered ubiquitin-associated genetic mutation seven months ago. Herein we would like to comment about this rare case.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects both upper and lower motor neurons in the motor cortex of the brain, brainstem, and spinal cord. Because of the progressive degeneration of motor neurons, ALS eventually leads to their death. Degenerating motor neurons develop protein-rich inclusions in their cell bodies and axons, which may be due to, at least in part, defects in protein degradation. Recently, focus on RNA metabolism and protein degradation disorders in familial ALS has intensified. The most frequently encountered disorders involve ubiquitin, superoxide dismutase (SOD1), TAR DNA-binding protein (TDP-43 or TARDBP), or fused in sarcoma (FUS) (1).

In recent years, ALS has been thought to not be a monotypic disease but a syndrome consisting of diseases caused by a series of non-overlapping mechanisms. Multiple genetic and environmental factors have been implicated in ALS pathogenesis (1,2). Several theories related to the etiopathogenesis of ALS have been proposed, including oxidative stress, mitochondrial dysfunction, excitotoxicity, defective axonal transport, and abnormal protein aggregation; however, the true etiopathogenesis is not known with certainty (3). Majority of ALS cases are sporadic. Genetic testing of sporadic cases has shown that genetic transmission occurs in 5% of all ALS cases (familial ALS). SOD1 was the first best studied gene responsible of approximately 20% of familial cases. In recent years, numerous genes other than SOD1 have been identified that are responsible for familial forms of ALS. Today, hexanucleotide expansion in the C9orf72 gene is the most common mutation (20–40%) in all populations studied. Genetic transmission in familial ALS is usually autosomal dominant with differing degrees of penetrance (4,5).

From the 1990s, ubiquitin-positive inclusions have been identified in the motor neurons of autopsied ALS patients. Ubiquitin 2 is a member of the ubiquitin-like protein family (ubiquilins). The ubiquitin LN2 (UBQLN2) protein plays a role in the ubiquitin–proteasome pathway that is responsible for protein degradation. Changes in this protein lead to the intracellular precipitation of proteins that self-interact, and cell death results from the excessive deposition of these precipitants. Correct protein folding is vital not only for the protein itself but also for the cell and whole organism. Cellular stress and aging unfavorably affect the proteostasis and balance of this complex network. Cellular pathology and risk of disease are considerably enhanced, particularly at the neuronal level, when a certain threshold is exceeded (6,7).

The incidence of different ubiquitin gene mutations in ALS patients varies. A recent study has revealed that UBQLN2 plays a pathogenic role in X-linked ALS-frontotemporal dementia (ALS/FTD) (8).

A 63-year-old female patient presented with frequent, sometimes injurious, falls that began five years ago and that were accompanied by speech disorders as well as by amnesia and changes in mood and temperament six months later. Her personal history was unremarkable. Her four sisters and one niece (daughter of a healthy brother) exhibited the same symptoms, which began around the age of 50 years. Three of the sisters and the niece died within four to seven years. The disease had a better prognosis in the living sister. Her mother died at the age of 52 years due to tuberculosis, and her father died at the age of 72 years due to myocardial infarction.

During her neurological examination, her speech was slow and dysarthric, cooperation was barely established, proximal muscle strength of the lower extremities was scored 3/5, distal muscle strength was scored 4, deep tendon reflexes in the upper extremities were scored 3, patellar reflex was scored 3, and the Achilles reflex was scored 4. The plantar skin reflex test produced an extensor response on the left side. She could stand up with assistance and exhibited steppage and ataxic gait. There was no fasciculation or tremor; strength of the tongue was excellent, and sensations of position and vibration were normal.

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Upon laboratory examination, creatine kinase levels were two-fold higher than the threshold for normal (413, N:30–200 IU/L). Sensory and motor nerve conduction studies were normal. Needle EMG of thoracic and lumbar muscles revealed fibrillations and positive sharp waves as well as motor unit potentials with increased amplitudes, prolonged durations, and decreased voluntary recruitment. Cranial, cervical, and lumbar spinal magnetic resonance images were unremarkable. Psychometric tests revealed severe cognitive impairment (Mini-mental State Examination score: 11, N:24–30). On neuropsychological examination, notable frontal axis-related symptoms, accompanied by extreme verbal and nonverbal memory impairment and visual-spatial dysfunction, were observed. Memory impairment was present in all phases of recording, learning, and recall. The presence of dementia and history of the family led us to make a preliminary differential diagnosis of Huntington's disease (HD). However, genetic analysis revealed that the number of trinucleotide repeats in the HD gene was within the normal range. In the present case, a diagnosis of ALS was considered based on the anamnesis, clinical and neurological examinations, and EMG findings (El Escorial criteria). Familial ALS/FTD was diagnosed because of the presence of similar cases in the family, and the index case and living siblings underwent genetic examination. As a result of the genetic examination, the Serin340Isoleucine (S340I) mutation, which is rarely encountered and is usually accompanied by dementia, was identified in the UBQLN2 gene. The living affected sister (II.7), living healthy brother (II.4), and healthy daughter of this brother (III.12) were shown to be gene-positive. The oldest brother, healthy son of the patient, youngest sister of the patient, and stepsister of the patient did not have the mutation. This suggests that the mutation was inherited from the mother and not the father. The sequencing of UBQLN2-S340I in this case indicated the presence of an X-linked ALS/FTD with incomplete penetrance in this family (Figure 1). The patient was treated with riluzole and anti-dementia drugs.

In majority of cases of familial ALS, an autosomal dominant inheritance pattern has been described, although recessive and X-linked forms also exist. In hereditary cases, the motor phenotypes of familial and sporadic ALS cannot be distinguished, suggesting shared molecular mechanisms. Familial ALS is phenotypically and genetically heterogeneous, although the clinical and pathological signs of familial and sporadic cases exhibit many similarities. The Mendelian inheritance of ALS indicates that the expressed genetic defects become selectively toxic. However, gene defects subtly manifest over many years. Therefore, symptoms in familial cases usually occur during adulthood, similar to those in sporadic cases (3,4,9). The symptoms in our index case and her family members also began to present around the fifth decade of life. The course of familial ALS is slower than that of sporadic cases, although a generalization is misleading. In our case, neurodegeneration had been ongoing for five years.

Cognitive function is generally protected in majority of patients. The incidence of ALS together with cognitive impairment is variable. Although some patients (approximately 5%) also develop FTD (10), 30–50% of patients also have subtle cognitive changes that can be revealed by detailed neuropsychological testing. Cognitive changes in ALS patients that result from degeneration in the front and side parts of the brain are not a psychiatric illness. Some patients present with frontotemporal dementia, and executive function-dependent tasks are difficult for such patients (8,9,11). We identified a UBQLN2 gene mutation accompanying dementia in the X-linked ALS patients. Dementia was a prominent feature in all UBQLN2-linked family members. There were also asymptomatic subjects in the family of the index case, even though they carried the mutation. Asymptomatic subjects who carry a UBQLN2 gene mutation, although rare, have been reported in the literature.

Protein aggregates/inclusions have been recognized in several neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, tauopathies, and synucleinopathies (12). Ubiquitin-positive inclusions are considered to be a hallmark of ALS pathology. A small subgroup of ALS patients exhibit mutations in ubiquitin and related proteins (8,13). We identified a novel UBQLN2 mutation in an ALS/FTD patient, and this condition supports the hypothesis that UBQLN2 mutations lead to ALS/FTD phenotypes.

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REFERENCES

- Byrne S, Walsh C, Lynch C, Bede P, Elamin M, Kenna K, McLaughlin R, Hardiman O. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2011; 82:623-627. [CrossRef]

2. Eisen A. Amyotrophic lateral sclerosis: A review". BCMJ 2002; 44:362-366.
3. Gordon P. Amyotrophic lateral sclerosis. Pathophysiology, diagnosis and management. CNS Drugs 2011; 25:1-15. [\[CrossRef\]](#)
4. Tiwari A, Hayward LJ. Familial amyotrophic lateral sclerosis mutants of copper/zinc superoxide dismutase are susceptible to disulfide reduction. J Biol Chem 2003; 278:5984-5992. [\[CrossRef\]](#)
5. Bruijn LI, Houseweart MK, Kato S, Anderson KL, Anderson SD, Ohama E, Reaume AG, Scott RW, Cleveland DW. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. Science 1998; 281:1851-1854. [\[CrossRef\]](#)
6. Dunlop RA, Cox PA, Banack SA, Rodgers KJ. The non-protein amino acid BMAA is misincorporated into human proteins in place of l-serine causing protein misfolding and aggregation. PLoS ONE 2013; 8:e75376.
7. Lahut S, Ozes B, Agar S, Basak AN. TDP-43 Proteinopatileri: Nörodejeneratif konformasyon bozukluğu hastalıklarında yeni bir oyuncu. Turk Norol Derg 2012; 18:1-10. [\[CrossRef\]](#)
8. Deng HX, Chen W, Hong ST, Boycott KM, Gorrie GH, Siddique N, Yang Y, Fecto F, Shi Y, Zhai H, Jiang H, Hirano M, Rampersaud E, Jansen GH, Donker-vooort S, Bigio EH, Brooks BR, Ajroud K, Sufit RL, Haines JL, Mugnaini E, Pericak-Vance MA, Siddique T. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature 2011; 477:211-215. [\[CrossRef\]](#)
9. Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, Gibbs JR, Brunetti M, Gronka S, Wu J, Ding J, McCluskey L, Martinez-Lage M, Falcone D, Hernandez DG, Arepalli S, Chong S, Schymick JC, Rothstein J, Landi F, Wang YD, Calvo A, Mora G, Sabatelli M, Monsurro MR, Battistini S, Salvi F, Spataro R, Sola P, Borghero G; ITALSGEN Consortium, Galassi G, Scholz SW, Taylor JP, Restagno G, Chiò A, Traynor BJ. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron 2010; 68:857-864. [\[CrossRef\]](#)
10. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol 2007; 6:994-1003. [\[CrossRef\]](#)
11. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-Linked FTD and ALS. Neuron 2011; 72:245-256. [\[CrossRef\]](#)
12. Kuzuhara S, Kokubo Y. P3-146: Marked increase of parkinsonism dementia (P-D) phenotypes in the high incidence amyotrophic lateral sclerosis (ALS) focus in the Kii peninsula of Japan. Alzheimer's Dementia 2006; 2:S417.
13. Aguzzi A, O'Connor T. Protein aggregation diseases: pathogenicity and therapeutic perspectives. Nat Rev Drug Discov 2010; 9:237-248. [\[CrossRef\]](#)