

Rapid progressive ALS in a patient with a *DNAJC7* loss-of-function mutation

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Recently, *DNAJC7* was found to be associated with amyotrophic lateral sclerosis (ALS) in a single large-scale exome sequencing study.¹ Multiple protein-truncating variants were detected in individuals with ALS that were absent in control subjects.¹ *DNAJC7* encodes a member of the DnaJ heat-shock protein family (HspP40), which functions in protein homeostasis, including protein folding and degradation.² To validate the pathogenic role of *DNAJC7* in ALS and further understand the relevant clinical features, we screened a Taiwanese ALS cohort for *DNAJC7* mutations.

Methods

A consecutive series of 325 unrelated individuals (191 men and 134 women) with ALS diagnosed by the revised EL Escorial criteria 2015 were enrolled into the study.³ The average at disease onset was 54.3 (range 19–89) years. Seventy patients (21.5%) were affected by a bulbar-onset ALS, 39 patients (12%) had an ALS family history, 64 individuals carried a mutation in other ALS disease genes, such as *SOD1*, *C9ORF72*, *TARDBP*, or *FUS*, and 254 patients had an apparently sporadic ALS without any known mutation for ALS. Genomic DNA was extracted from peripheral blood samples. Mutation analyses of the coding region of *DNAJC7* were performed by PCR amplification and Sanger sequencing. The amplicon sequences were compared with the reference *DNAJC7* coding sequence (NM_003315.4). All participants provided a written informed consent, and this study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Results

Mutational analysis of *DNAJC7* in the 325 ALS patients revealed only one heterozygous truncating frameshift variant, c.401_402delAA (p.Q134Rfs*6) (figure, A), in one single individual with apparently sporadic ALS. Neither this variant nor other *DNAJC7* loss-of-function (LOF) variant was found in the 1,517 ethnically matched control genomes in the Taiwan Biobank database (taiwanview.twbiobank.org.tw). The p.Q134Rfs*6 variant was also absent in the Genome Aggregation Database (gnomAD v2.1.1; gnomad.broadinstitute.org). The variant was predicted as a disease-causing mutation by 2 bioinformatics tools, MutationTaster (mutationtaster.org)⁴ and Combined Annotation Dependent Depletion (CADD v1.6; cadd.gs.washington.edu)⁵ with the CADD PHRED score 31.

The gentleman carrying the *DNAJC7* mutation had an initial symptom of left hand weakness at age 61 years. Neurologic examinations at age 62, approximately 1 year after the disease onset, revealed tongue atrophy with fasciculation, weakness and atrophy with fasciculation in the bilateral upper extremities (muscle strength of 2–3 of 5 according to the Medical Research Council scale), a mild degree of weakness of the left hip flexor (4/5), diminished deep tendon reflexes, and normal

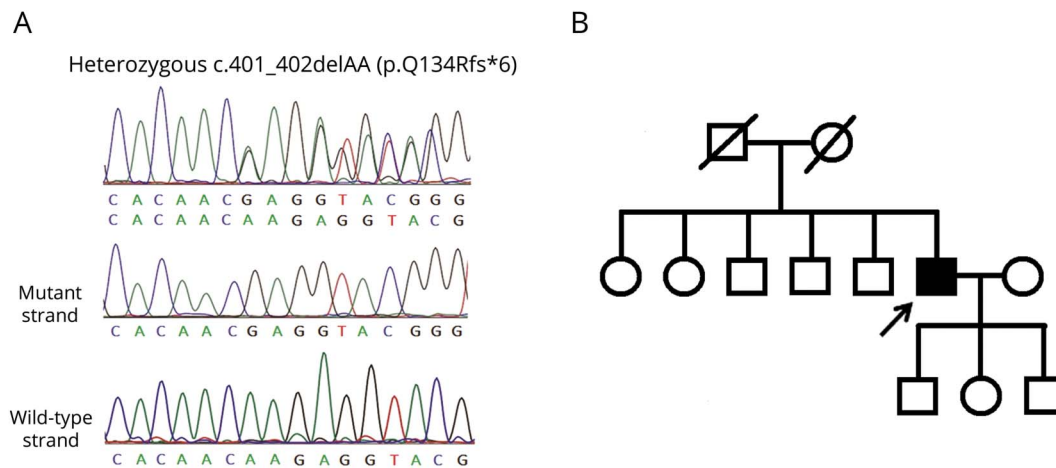
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Figure The *DNAJC7* mutation and pedigree of the patient with ALS



(A) Sanger sequence traces of the *DNAJC7* c.401_402delAA (p.Q134Rfs*6) mutation identified in the ALS patient in this study. The heterozygous frameshift mutations are clearly demonstrated by sequencing the TA-subcloned PCR fragments. (B) The pedigree structure of the ALS patient with the *DNAJC7* mutation. Open symbol: unaffected; filled symbol: affected; symbol with diagonal line: deceased subjects; square: male; circle: female; arrow: the proband. ALS = amyotrophic lateral sclerosis.

cognitive function. The symptoms deteriorated rapidly in the following 6 months, and the patient developed bilateral lower limbs weakness and respiratory distress requiring noninvasive ventilation support. The Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) scores were 38 at age 62 and dropped to 13 six months later.⁶ The patient did not carry any other mutation related to ALS and denied having a family history of ALS (figure, B).

Discussion

We identified a *DNAJC7* LOF mutation, p.Q134Rfs*6, in a patient with apparently sporadic ALS. Its pathogenicity was supported by the following findings. First, *DNAJC7* p.Q134Rfs*6 is absent in the 1,517 ethnically matched Taiwanese control genomes and the gnomAD. Second, the mutation was predicted as pathogenic by Mutation Taster and CADD programs. Furthermore, *DNAJC7* p.Q134Rfs*6 is a truncating frameshift mutation, which putatively results in a truncated, often unstable protein product that compromises *DNAJC7* functions. Similar *DNAJC7* LOF mutation, p.R156*, has been demonstrated with significantly reduced protein production in vitro.¹

The *DNAJC7* p.Q134Rfs*6 mutation was identified in one of the 254 unexplained sporadic ALS patients (0.4%). In another recent study, *DNAJC7* protein-truncating variants were identified in 8 out of 5,095 (0.16%) ALS patients.¹ These findings suggest that *DNAJC7* mutations are not a common cause of ALS.

The clinical features of ALS associated with *DNAJC7* LOF mutations remain elusive. Our patient had a typical spinal-onset ALS but a rapidly progressive disease course with 35 points decline of the ALSFRS-R scores during the 18 months after disease onset. According to the PRO-ACT database, the

average rate of the ALSFRS-R decline of the ALS patients was 1.02 points per month.⁷ Lack of ALS family history of the patient suggests that *DNAJC7* may be a risk gene or mendelian disease gene with reduced penetrance for ALS. Regrettably, we cannot approach the patient's siblings and parents, and this is a limitation of the present study. Further studies are warranted to elucidate the role and phenotypic features of *DNAJC7* mutations in ALS.

In conclusion, we identified a patient carrying a *DNAJC7* p.Q134Rfs*6 mutation and suffering from a rapidly progressive spinal-onset ALS. The present study underlines the pathogenic role of *DNAJC7* LOF mutation in ALS.

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Disclosure

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Appendix Authors

Name	Position	Contribution
Kang-Yang Jih, MD, PhD	Taipei Veterans General Hospital, Taiwan	Study coordination and drafting the manuscript
Pei-Chien Tsai, PhD	National Chung Hsing University, Taichung, Taiwan	Analysis and interpretation of the data and revised the manuscript
Yu-Shuen Tsai, PhD	National Yang-Ming University, Taipei, Taiwan	Analysis and interpretation of the data and revised the manuscript

References

1. Farhan SMK, Howrigan DP, Abbott LE, et al. Exome sequencing in amyotrophic lateral sclerosis implicates a novel gene, DNAJC7, encoding a heat-shock protein. *Nat Neurosci* 2019;22:1966–1974.
2. Qiu XB, Shao YM, Miao S, Wang L. The diversity of the DnaJ/Hsp40 family, the crucial partners for Hsp70 chaperones. *Cell Mol Life Sci* 2006;63:2560–2570.
3. Ludolph A, Drory V, Hardiman O, et al. A revision of the El Escorial criteria—2015. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:291–292.

Appendix (continued)

Name	Position	Contribution
Yi-Chu Liao, MD, PhD	Taipei Veterans General Hospital, Taiwan	Patient enrollment, acquisition of data, interpreted the data, and revised the manuscript
Yi-Chung Lee, MD, PhD	Taipei Veterans General Hospital, Taiwan	Designed and conceptualized the study, patient enrollment, acquisition of data, interpreted the data, and revised the manuscript

4. Schwarz JM, Cooper DN, Schuelke M, Seelow D. MutationTaster2: mutation prediction for the deep-sequencing age. *Nat Methods* 2014;11:361–362.
5. Kircher M, Witten DM, Jain P, O’Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet* 2014;46:310–315.
6. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *BDNF ALS Study Group (Phase III)*. *J Neurol Sci* 1999;169:13–21.
7. Atassi N, Berry J, Shui A, et al. The PRO-ACT database: design, initial analyses, and predictive features. *Neurology* 2014;83:1719–1725.

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