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

Kang-Yang Jih, MD, PhD, Pei-Chien Tsai, PhD, Yu-Shuen Tsai, PhD, Yi-Chu Liao, MD, PhD, and Yi-Chung Lee, MD, PhD

Correspondence
Dr. Lee
ycli@vghtpe.gov.tw

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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

From the Department of Neurology (K.-Y.J., Y.-C. Liao, Y.-C. Lee), Taipei Veterans General Hospital; Department of Neurology (K.-Y.J., Y.-C. Liao, Y.-C. Lee), Brain Research Center (Y.-C. Liao, Y.-C. Lee), and Center for Systems and Synthetic Biology (Y.-S.T.), National Yang-Ming University, Taipei; and Department of Life Sciences (P.-C.T.), National Chung Hsing University, Taichung, Taiwan.

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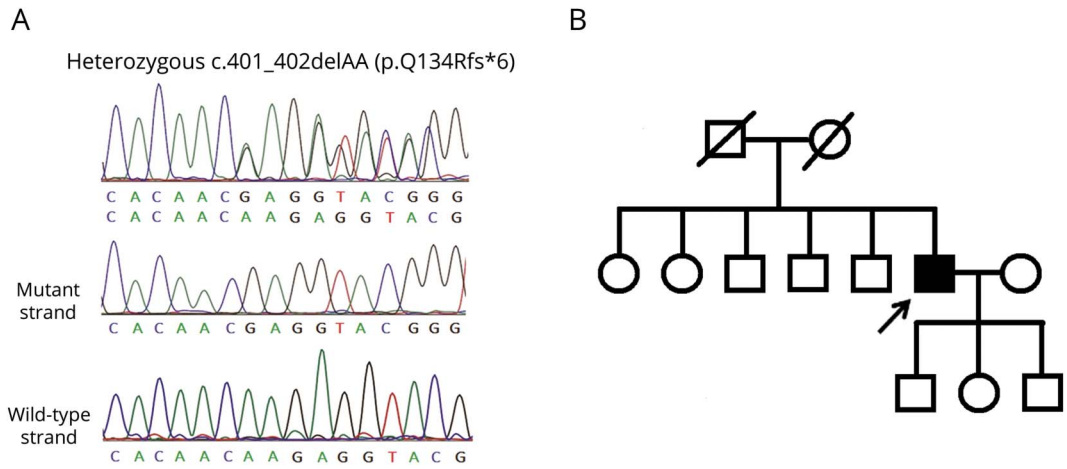
Figure The DNAJC7 mutation and pedigree of the patient with ALS



(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
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

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