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ORIGINAL ARTICLE

Reduced-penetrance Huntington's disease-causing alleles with 39 CAG trinucleotide repeats could be a genetic factor of amyotrophic lateral sclerosis

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Abstract

Background: Expanded *HTT* alleles with 40 or more CAG repeats were recently found to be a rare cause of frontotemporal dementia and amyotrophic lateral sclerosis (ALS) spectrum diseases. The aim of this study was to investigate the role of *HTT* repeat expansions in a Taiwanese cohort with ALS.

Methods: We analyzed the numbers of CAG repeats in exon 1 of *HTT* in a cohort of 410 Taiwanese patients with ALS and 1514 control individuals by utilizing polymerase chain reaction and amplicon fragment length analysis.

Results: Only one of the 410 ALS patients carried a reduced-penetrance HD-causing allele with 39 CAG repeats, and none had an expanded *HTT* CAG repeats ≥40. The patient presented with rapidly progressive bulbar-onset ALS with disease onset at the age of 64 years. He had neither chorea nor cognitive impairment. He had a family history of chorea, but no other family member manifested with ALS. None of the 1514 control individuals carried an *HTT* expanded allele with CAG repeats larger than 37 repeats.

Conclusion: The *HTT* allele with 39 CAG repeats could be a genetic factor linked to ALS susceptibility.

Keywords: Amyotrophic lateral sclerosis; Huntington's disease; *HTT*; Polyglutamine expansion

1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that results in both upper and lower motor neuron loss. Clinically, ALS manifests with progressive limb weakness, muscle atrophy, and bulbar palsy. Most patients who suffer from ALS die of respiratory failure or other complications within 5 years of disease onset. To date, there are more than 40 ALS causative or associated genes reported in previous literature.[1] A known ALS-associated gene can be identified in approximately 15% of sporadic ALS cases and 70% of familial cases.[2]

Short tandem repeat expansions account for a major group of disease-related variants of ALS, including the most common pathogenic mutations (GGGGCC hexanucleotide repeats in *C9ORF72*).[2] In addition, the CAG trinucleotide repeats in *ATXN1* and *ATXN2* as well as the CAG/CAA trinucleotide repeats in *TBP* have also been implicated in ALS.[3–5] The CAG repeat expansion of *HTT,* another pathogenic tandem repeat expansion, was once thought to be unassociated with ALS.[6,7] However, a recent large-scale study based on two ALS and frontotemporal dementia (FTD) cohorts has provided new evidence supporting that pathogenic *HTT* repeat expansions are a rare cause of FTD and ALS spectrum diseases.[8] The study revealed that the percentage of FTD/ALS patients carrying a pathogenic expanded *HTT* allele with 40 or more CAG repeats, despite being rare, is significantly higher than that in control subjects.[8] This finding suggested that expanded *HTT* alleles with 40 or more CAG repeats may cause ALS.

HTT is the causative gene of Huntington's disease (HD). It encodes the protein Huntingtin, whose physiological function remains incompletely understood. *HTT* contains a segment of CAG trinucleotide repeats with variable lengths in exon 1. Alleles with ≥36 CAG repeats are considered pathogenic. Reduced-penetrance HD-causing alleles are those with 36 to 39 CAG repeats, whereas alleles with ≥40 CAG are full-penetrance HD-causing alleles. Typical symptoms of HD include chorea, cognitive impairment, and psychiatric disorders, which are drastically different from the symptoms of ALS, which commonly manifest with progressive limb weakness, muscle atrophy, fasciculation, and upper motor neuron signs such as hypereflexia. Interestingly, patients with genetically confirmed HD presenting with clinical features that mimic ALS have been described in several case series.[9] Among 11 such cases reported between 1996 and 2013, nine patients presented with both chorea and

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muscle weakness, whereas two others presented with only muscle weakness.[10]

In this study, we analyzed *HTT* CAG repeat sizes in an ALS cohort consisting of 410 Taiwanese patients of Han Chinese ethnicity to further understand the role of *HTT* CAG repeat expansion in ALS.

2. METHODS

2.1. Study subjects

In this study, we enrolled 410 unrelated individuals (248 men and 162 women) who were diagnosed with probable or definite ALS based on the revised El Escorial criteria.[11] All participants were of Han Chinese descent. They were recruited from the Neurology Services of Taipei Veterans General Hospital, which is a 3096-bed medical center in Taiwan that serves both regular citizens and veterans and accepts both self-referred patients and referrals from outside hospitals. These 410 patients were selected from a consecutive series of 477 unrelated ALS patients after excluding mutations in *SOD1* (20 patients), *C9ORF72* (18), *TARDBP* (16), *FUS* (8), *CCNF* (2), *OPTN* (1), *MATR3* (1), and *TBK1* (1). The average age at disease onset was 55.8 years (range 15-89 years) for the 410 ALS patients. Two hundred forty-eight (60.5%) patients were male. Eleven patients (2.7%) had a positive family history of ALS, and 399 (97.3%) were apparently sporadic cases. Seventy-seven patients (18.8%) suffered from bulbar-onset ALS, and 211 (51.5%) had disease onset from the upper limbs. Another group of 1514 control individuals was enrolled from Taipei Veterans General Hospital. Most of them were healthy individuals who accompanied a patient with neurological diseases other than ALS or HD to visit our hospital. Neurological examinations were performed with normal findings before the recruitment of these control subjects. The mean age of the control group at recruitment was 56.6 years (range 19-100 years). This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan. Informed consent was obtained from all study participants or their families for those who were unable to provide written consent.

2.2. Genetic analysis of the HTT CAG trinucleotide repeat size

Peripheral white blood cells were harvested for genomic DNA extraction. Polymerase chain reaction (PCR) and amplicon fragment length analysis were used to analyze the *HTT* CAG trinucleotide repeat length. The CAG repeat regions were amplified by PCR with one primer of the fluorescently labeled primer pair. The forward and reverse sequences of the PCR primers were 5'-6FAM-atgaaggccttcgagtccctcaagtccttc-3' and 5'-ggcggtggcggctgttgctgctgctgctgc-3', respectively. Fragment length analysis of the amplicons was conducted on an ABI Prism 3730 × l Genetic Analyzer (Applied Biosystems, Waltham, MA, USA) using the GeneScan 500 LIZ dye Size Standard (Applied Biosystems) and GeneMapper software (v3.7; Applied Biosystems). The size of the alleles was used to calculate the CAG repeat numbers.

2.3. Calculation of the caudate volumes

The high-resolution T1-weighted 3T MRI scans were processed with the Statistical Parametric Mapping (SPM) software package version 12 (SPM12, Wellcome Centre of Human Neuroimaging, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/) in a MATLAB environment (R2019b; MathWorks, Natick, MA, USA). The native T1-weighted images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid space (CSF) and normalized into Montreal Neurological Institute space using the classical unified segmentation approach.[12] The total intracranial volume was determined from the sum of the GM, WM, and CSF volumes using the get totals script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m.) written by SPM developers. To calculate the volume of each of the regions of interest (ROIs), such as the caudate nucleus, we applied the templates from automated anatomical labeling atlas 3 (AAL3)[13] and built the related masks to crop the volume of each ROI through the MarsBaR toolbox.[14] The volumes of each ROI, again, were obtained with the get totals script.

3. RESULTS

The number of *HTT* CAG trinucleotide repeats in the 410 unrelated ALS patients ranged from 9 to 39, and the allele with 17 CAG repeats was the most common, accounting for 55% of the total alleles. For the 1514 control individuals, the length of CAG repeats ranged from 9 to 37, and the allele with 17 CAG repeats was also the most prevalent, accounting for 58% of the total alleles. None of the individuals in either group carried a pathogenic *HTT* allele with full penetrance (≥40 CAG repeats). However, one ALS patient (patient T531) harbored a reduced-penetrance HD-causing allele with 39 CAG repeats. The size of the longest *HTT* CAG repeats in the control group was 37 repeats, which was identified in two individuals. The distribution of the sizes of the *HTT* CAG repeats for the ALS patients and controls are shown in Fig. 1 and Supplementary Table 1, http://links.lww.com/JCMA/A164.

Patient T531 carried an *HTT*-expanded allele with 39 CAG repeats and a wild-type allele with 17 repeats. He suffered from bulbar-onset ALS with an initial presentation of progressive dysarthria at age 64 years, followed by weakness of the proximal muscles of the upper limbs. Neurological examination at age 65 years revealed the marked weakness of bilateral shoulder abduction (Medical Research Council score, MRC 3/5) and milder weakness of the lower limbs (MRC 4/5). Severe tongue and shoulder girdle muscle atrophy with fasciculation was also noted (Fig. 2B, C). Tendon reflexes were normoactive (2+) in the upper and lower limbs, yet bilateral plantar reflexes showed dorsiflexion responses. No involuntary movement was found during the examination. Brain and spinal cord magnetic resonance imaging (MRI) only showed diffuse atrophic changes in the brain (Fig. 2D, E). The caudate volume of this patient was 3.7 cm^3. According to a previous study, the average caudate volume of 10 control individuals with an average age of 65.5 years old was 8.29 cm^3.[15] Similarly, another study showed that the average caudate volume was 8.88 cm^3 in a group of 30 control individuals with an average age of 44.6 years old.[16] Therefore, the caudate volume of this patient was indeed smaller, which may suggest early pathologic changes in Huntington's disease[17] (Fig. 2D). The patient scored 86 out of 100 on the Cognitive Abilities Screening Instrument test,[18] indicating intact cognitive function. An electrophysiological study showed widespread active denervation and chronic neurogenic changes in the muscles of the bulbar, cervical, thoracic, and lumbar regions. The symptoms deteriorated relentlessly. His initial Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) score was 35 at the age of 65 years and dropped to 28 6 months later. The patient died of pneumonia at age 66 years, 23 months after symptom onset. It is worth mentioning that the patient had a positive family history of chorea, whereas none of the affected members received the genetic diagnosis (Fig. 2A). None of the family members had been diagnosed with ALS.

4. DISCUSSION

In this study, we reported an ALS patient carrying an *HTT* allele with 39 CAG repeats. This patient presented with a typical ALS

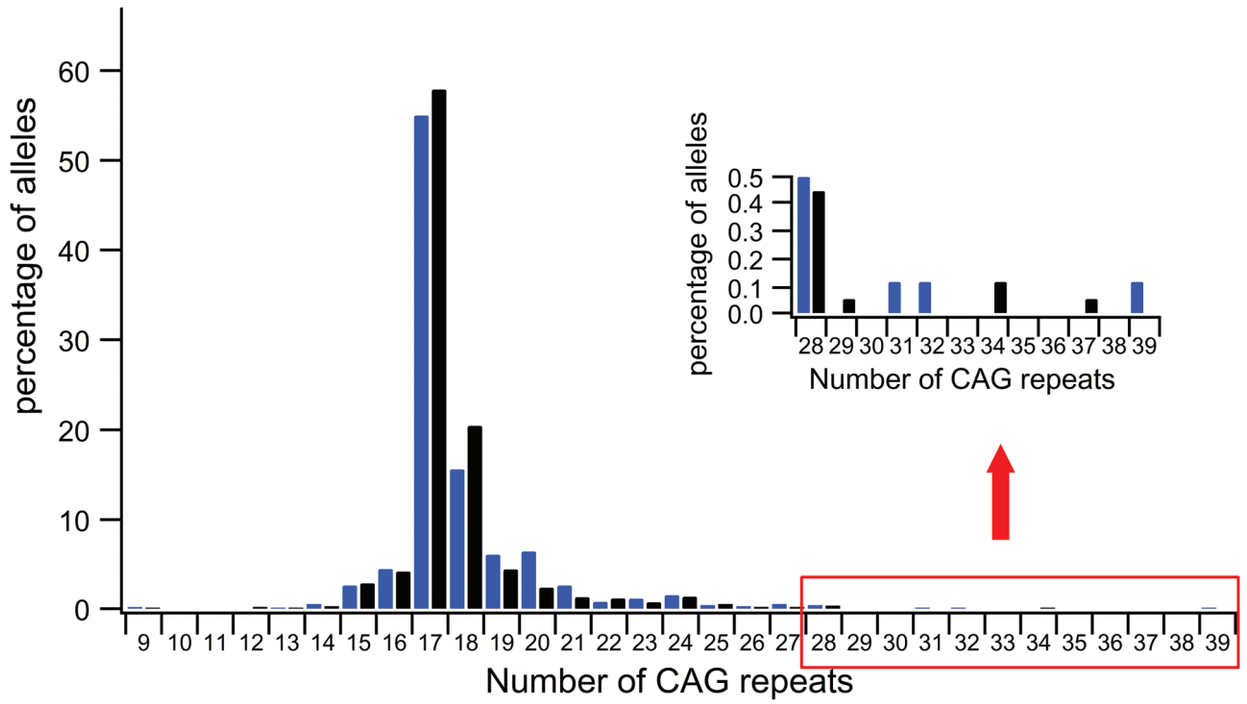

Fig. 1 Investigation of *HTT* CAG repeats in Taiwanese patients with amyotrophic lateral sclerosis (ALS) and control individuals. The distribution of the sizes of *HTT* CAG repeats in 410 patients with ALS (blue bars) and 1514 healthy controls (black bars).

phenotype without any HD symptoms, including chorea and cognitive dysfunction. Furthermore, we analyzed *HTT* CAG repeats in 1514 control individuals, and none of them had an *HTT* allele with more than 37 CAG repeats. These findings indicate that, in addition to full-penetrance HD-causing alleles, reduced-penetrance HD-causing alleles with 39 CAG repeats could also be a genetic factor linked to ALS susceptibility.

According to the literature reports, there have been 14 ALS cases found to carry a pathogenic HD-causing allele. All of the cases had an *HTT* allele with ≥39 CAG repeats. Nine of the 14 cases also had chorea. Pure ALS without other HD-related neurological manifestations has been reported in three cases.[8–10] Among the nine patients presenting with both chorea and ALS, five patients had detailed chronological information about the initial and subsequent symptoms.[9,10] Symptoms of HD and ALS, such as chorea and limb weakness, appeared within 2 years in all five aforementioned cases, implying that HD and ALS are closely related and likely result from a common pathophysiological process. Of note, the patient in our cohort had a strong family history of chorea. In addition, as reported in a previous study, patients carrying *HTT* alleles with 39 CAG repeats and manifesting a pure ALS phenotype also had a family history of HD.[9] This finding suggested that chorea and ALS may derive from a common genetic factor.

There has been a long debate regarding the role of reduced-penetrance HD-causing alleles (36-39 CAG repeats) in HD because a significant proportion of symptom-free carriers have been identified in the general population.[19] It is generally accepted that the age of onset of HD is inversely correlated with the number of CAG repeats.[20] A previous study analyzing a large HD cohort suggested that the lifetime risk of developing HD for patients carrying an *HTT* allele with 39 CAG repeats was as high as 79%.[21] Another observational study suggested that the mean age of disease onset of patients carrying an *HTT* allele with 39 CAG repeats was 62.1 years.[22] Both lines of evidence indicate that, for those carrying an *HTT* allele with 39 CAG repeats, there is a high possibility of developing HD in their lifespan. Unlike *HTT* alleles with 36-38 CAG repeats that occur with a relatively high frequency in the general population, alleles with 39 CAG repeats are absent in a cohort of 7315 individuals from three general population-based cohorts in Canada, the United States, and the United Kingdom,[19] suggesting that such alleles are extremely rare in healthy subjects. The aforementioned evidence suggests that individuals harboring an *HTT* allele with 39 CAG repeats are more likely to develop phenotypes than individuals with an allele of 36-38 repeats. In other words, although the penetrance of HD is incomplete in individuals with an *HTT* allele with 39 CAG repeats, the lifetime risk of disease is apparently higher in individuals carrying an *HTT* allele with 39 CAG repeats than in those carrying 36-38 repeats. Of note, a previous case series reported a female patient carrying an *HTT* allele with 39 CAG repeats presenting with pure ALS at age 56 years,[9] which highly resembles the case we reported here. The case reported in this study would be the second one with 39 CAG repeats in *HTT* manifesting with an ALS phenotype. These findings indicate that 39 CAG repeats of *HTT* could indeed be associated with ALS.

Mechanistically, HD and ALS share several common pathways regarding their pathogenesis at the molecular level. For example, mitochondrial dysfunction and dysregulated transcription are known pathogenic mechanisms for both ALS and HD.[17,23,24] In addition, disruption of nuclear transport by mutant huntingtin aggregates has been proposed in HD.[25] Similarly, impaired nuclear membrane transport has been reported in ALS caused by *C9ORF72* hexanucleotide expansions.[26] In fact, *C9ORF72* hexanucleotide expansion is not only the most common genetic cause of ALS but also the most frequently identified genetic cause of HD phenocopies.[27] The cooccurrence of ALS and HD phenotypes in *C9ORF72* hexanucleotide expansion carriers lends support that chorea and

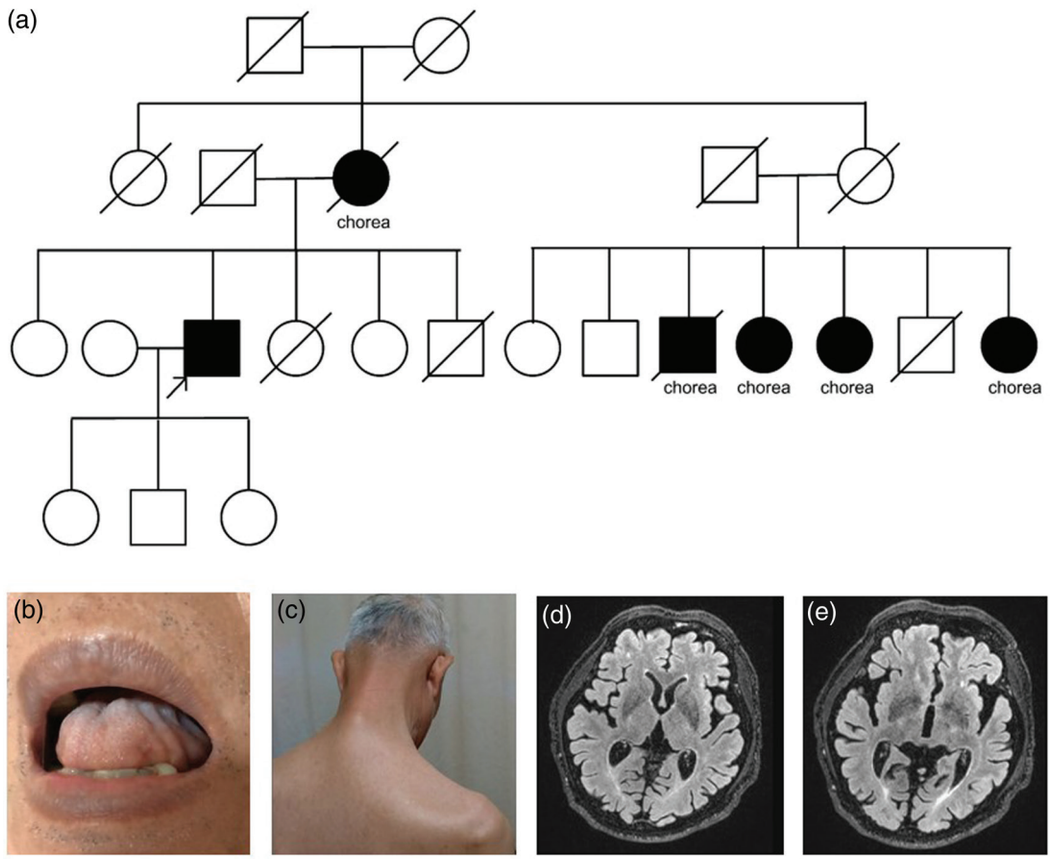

Fig. 2 (A) Pedigree of an amyotrophic lateral sclerosis (ALS) patient carrying reduced-penetrance Huntington's disease-causing alleles with 39 CAG repeats. The clinical pictures (B, C) of the ALS patient demonstrate tongue atrophy (B) and severe shoulder muscle atrophy (C). The brain MRI (D, E) images reveal mild diffused brain atrophy. The patient received an MRI examination and was photographed at age 65 years.

muscle weakness can result from the same genetic factor. A recent study also discovered that neuropathological diagnosis of ALS was over-represented in two cohorts of HD brain banks. This finding again implied an association between ALS and HD pathology.[28]

Indeed, another possibility is that ALS and pathogenic *HTT* repeat expansions discovered in this study are two independent events occurring together accidentally. However, in the Taiwanese population, the prevalence of ALS is approximately 2 per 100 000 people,[29] and as we demonstrated in this study, the possibility of carrying *HTT* alleles with ≥39 CAG repeats is less than 1 per 1514 in normal individuals. Based on both data, the estimated frequency for the two events (i.e., having ALS and carrying *HTT* alleles with ≥ 39 CAG repeats) occurring simultaneously would be less than 1 per 75 700 000 population. As a result, it is highly unlikely that the observation of *HTT* variants with ≥39 CAG repeats in our ALS patient was solely by chance.

Another important finding in this study is that ALS can be the first and only clinical presentation caused by *HTT* CAG repeat expansions with 39 repeats. Similar findings of intact striatum and absence of chorea were also reported in another ALS patient carrying a full-penetrance HD-causing allele.[8] One may argue that the patient may develop HD in future years should the patient live long enough. Indeed, a brain MRI with volumetric analysis of this ALS patient at age 65 years did show caudate atrophy, a radiological feature that usually precedes HD symptoms by decades.[17] Nonetheless, ALS was still the sole clinical presentation at 23 months after the diagnosis, when the patient died of pneumonia. This unique feature emphasizes the importance of encompassing the *HTT* gene in genetic surveys of ALS to avoid misdiagnosis. There are potential therapeutic implications because several clinical trials have been ongoing in HD patients. It is worth investigating whether such therapies could also be beneficial to ALS patients carrying pathogenic *HTT* CAG repeat expansions.

Our study had several limitations. First, the prevalence of ALS patients carrying an *HTT* allele with 39 CAG repeats was only 0.2% (1/410) in our cohort. The small case number makes it difficult to accurately estimate the real prevalence of such *HTT* variants in ALS patients and the risk of developing ALS in those carrying an *HTT* allele with 39 CAG repeats. Second, regrettably, we did not have the chance to examine the family members of the ALS patient carrying the *HTT* allele with 39 CAG repeats. Therefore, we cannot ascertain whether any of his family members also had motor neuron dysfunction and the expanded *HTT* allele, which may provide further support for the link between the *HTT* allele with 39 CAG repeats and ALS. Third, we did not have a cohort of HD patients for comparison of caudate volume with our patient. This can be achieved by the future development of a comprehensive HD cohort.

In conclusion, our findings suggest that, in addition to full penetrance HD-causing alleles with ≥40 CAG repeats, the expanded *HTT* allele with 39 CAG repeats may also contribute to ALS pathogenesis.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A164.

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