NOTCH2NLC GGC repeat expansion in a patient with amyotrophic lateral sclerosis

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Background

The GGC repeat expansion in 5'-untranslated region of *NOTCH2NLC* may cause neuronal intranuclear inclusion disease (NIID)[1], which has wide phenotypic spectrum. However, amyotrophic lateral sclerosis (ALS) is rarely associated with NIID.[2][3] Herein, we reported a ALS patient with the *NOTCH2NLC* mutation.

Case presentation

A 68 year-old man had insidious onset progressive dysarthria and dysphagia since 63 years old. He had normal sensation as well as muscle strength of four limbs. However, after 18 months, he began to have deteriorated muscle strength with atrophy, and fasciculation over four extremities. The patients' health condition worsening gradually and relentlessly. He became totally ADL-dependent and required variable positive airway pressure for ventilatory support since 67 years old. (Figure 1)

Neurological examinations at age 67 revealed severe tongue atrophy with fasciculation, decreasing muscle strength, atrophy over bilateral upper extremities. Besides, relative generalized increasing deep tendon reflexes was also noted. (Figure 2) Electromyography demonstrated active denervation with partial regeneration over four limbs, cervical and lumbar region. Brain magnetic resonance imaging revealed nonspecific cerebral white matter hyperintensities with no spinal cord compression.

Genetic survey revealed that the patient carried the two alleles with 92 and 15 GGC repeats within the 5' untranslated region of *NOTCH2NLC*, respectively. (Figure 3) He didn't have mutations in common ALS-associated genes, such as *SOD1*, *C9ORF72*, *TARDBP*, and *FUS*. Besides, he had no family history of ALS. (Figure 4)

Figure 1 Clinical presentation

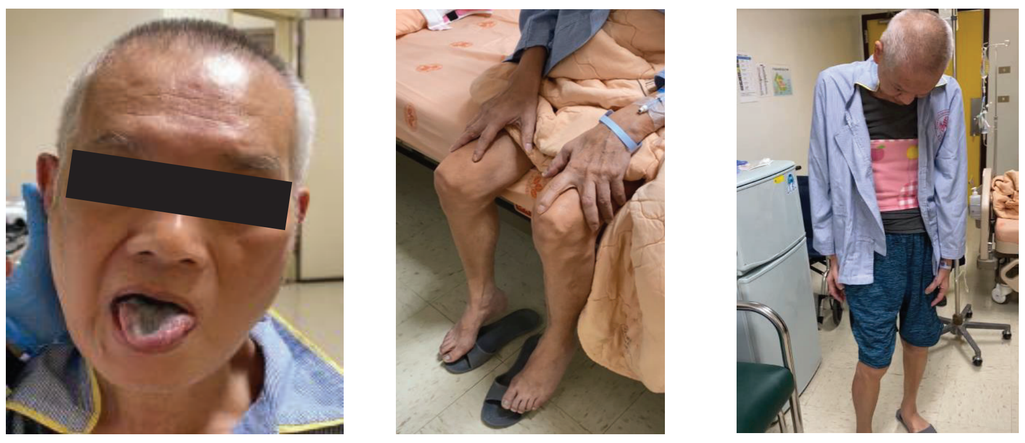


Figure 2 Neurological examination and clinical course

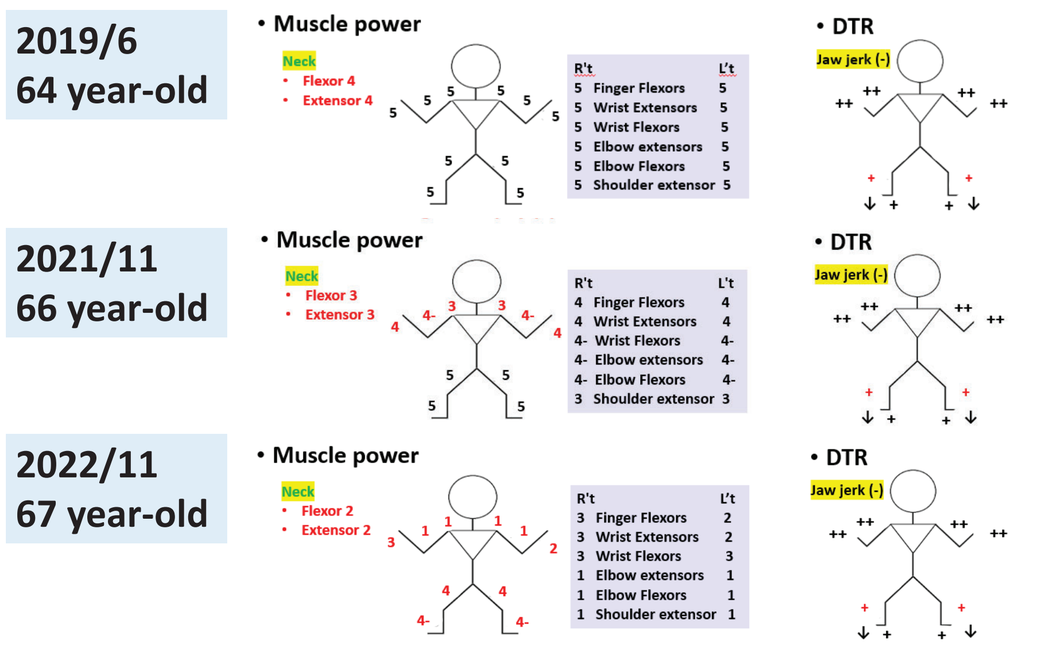


Figure 3 Fragment analysis and repeat-primed PCR analysis of *NOTCH2NLC* GGC repeat expansions

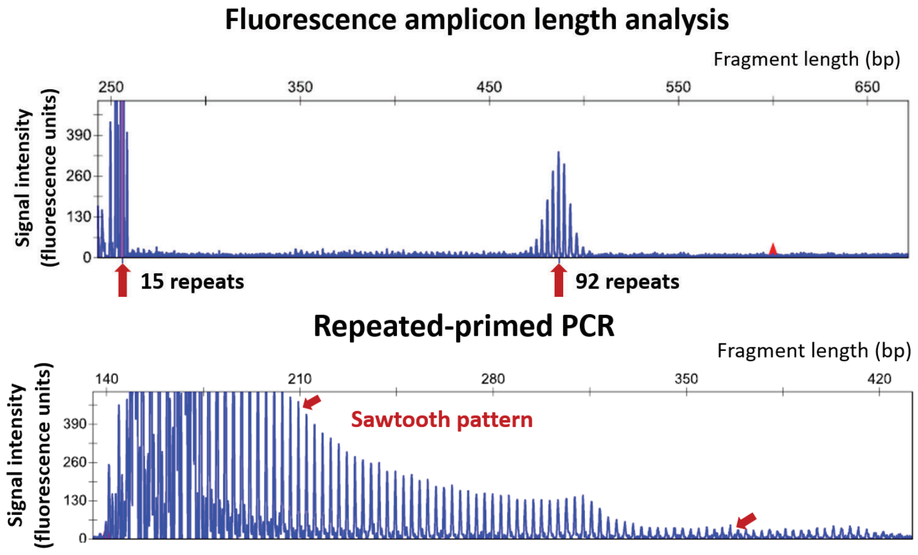
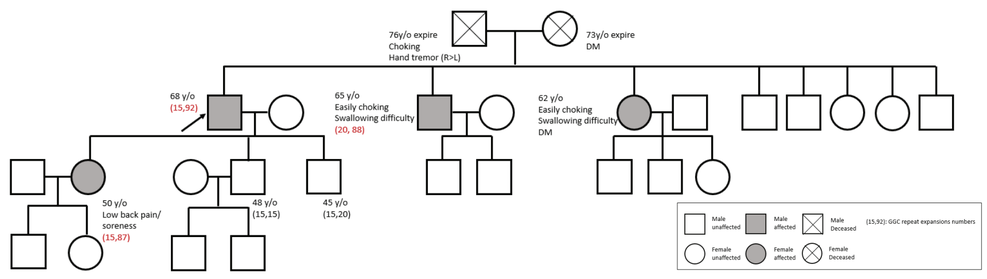


Figure 4 Family pedigree



Discussion

ALS is rarely associated with NIID. To date, only eight individuals with ALS and *NOCTH2NLC* GGC repeat expansion have been reported. [4][5][6][7] It is still uncertain that ALS is a rare clinical presentation of NIID or the *NOTCH2NLC* repeat expansion is a contributing factor of NIID.

Conclusion

Further large scale studies are necessary to understand the clinical and genetic features of patients with concomitant ALS and NIID and their individual roles in the disease pathogenesis.

References

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