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Letter to the Editor

C-terminal mutations in *SYNE1* are associated with motor neuron disease in patients with SCAR8

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Dear Editor,

Spinocerebellar ataxias (SCAs) are characterized by progressive cerebellar ataxia with or without non-cerebellar symptoms and classified as autosomal dominant, autosomal recessive, X-linked and mitochondrial. Spinocerebellar ataxia, autosomal recessive 8 (SCAR8) is caused by a mutation in *SYNE1* and originally reported as late-onset cerebellar ataxia with few extracerebellar symptoms in French-Canadian families [1]. Subsequent report [2] and multisenter studies [3,4] have described motor neuron disease (MND), mental retardation, autonomic nervous system dysfunction and extra-nervous system symptoms in patients with SCAR8, expanding its clinical spectrum. The mechanism why *SYNE1* mutations cause various nervous system dysfunctions including MND is unknown. Here, we report a novel *SYNE1* mutation in a patient with cerebellar ataxia accompanying MND. We review the previous reports about MND caused by *SYNE1* mutation.

A Japanese female presented with frequent falls at age 11 and difficulty writing and speaking at age 13. Her gait disturbance was slow progressing, and she needed a cane to walk at age 24 and a wheelchair at age 31. Neurological examination performed at age 32 revealed cerebellar ataxia and brisk tendon reflexes in the extremities. Subsequently, she showed progressive bulbar palsy and respiratory muscle weakness, initiating noninvasive positive pressure ventilation at age 38 and invasive ventilation at age 40. Neurological examination performed at age 45 revealed tongue atrophy with fasciculation, limb weakness with muscular atrophy, positive Babinski's sign and cerebellar ataxia in upper extremities. Mini Mental State Examination score was 28 and Frontal Assessment Battery score was 12. Needle electromyography (EMG) revealed very little or no spontaneous activity (fibrillation, positive sharp wave, and fasciculation potentials) in her limb muscles. Large amplitude, long duration motor unit potentials as well as reduced recruitment were shown in her limb muscles. The motor nerve conduction velocities were normal and compound muscle action potentials amplitude decreased. The sensory nerve conduction velocities and the sensory nerve action potentials were within the normal range. Magnetic resonance imaging (MRI) showed atrophy in the cerebellum and brainstem, and no abnormal intensities in the primary motor area and the pyramidal tract. Chest radiograph (Fig. 1A) and abdominal computed tomography (CT) (Fig. 1B, D) revealed elevated bilateral diaphragm and colon between liver and right hemidiaphragm which is called Chilaiditi syndrome.

Her parents were consanguineous, and her little sister had similar symptoms and clinical course. The proband's sister presented difficulty in walking and in stepping up and down stairs at age 19. She needed a cane to walk at age 25. She showed dysarthria and respiratory muscle weakness, initiating invasive ventilation at age 36. Neurological examination performed at age 44 revealed tongue atrophy with fasciculation, limb weakness with muscular atrophy, brisk deep tendon reflex in the exteremities, positive Babinski's sign and cerebellar ataxia in upper extremities. Needle EMG revealed large amplitude and long duration potentials without spontaneous activity in her limb muscles. Brain MRI showed atrophy in the cerebellum and brainstem without abnormal intensities in the primary motor area and the pyramidal tract. Chest radiograph revealed elevated bilateral diaphragm and Chilaiditi syndrome as with the proband (Fig. 1C).

Exome sequencing revealed a homozygous, stop-gain mutation in the *SYNE1* gene (NM_033071: c.19138C > T, p.R6380*). Using Sanger sequencing, we validated this mutation in the patient and her sister. The Combined Annotation Dependent Depletion (CADD) score of the mutation was 50 (http://cadd.gs.washington.edu/home). This mutation was absent in human genome variation databases, including the 1000 Genomes Project (http://www.internationalgenome.org), Exome Aggregation Consortium (http://exac.broadinstitute.org), and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar).

This patient with a novel nonsense mutation in the *SYNE1* gene presented with early-onset SCA accompanying MND. According to an original report [1], 26% of patients with SCAR8 exhibited brisk lower limb reflexes, although lower motor neuron disturbances were not described in this report. We first reported a SCAR8 patient with upper and lower motor neuron impairments, who presented with symptoms similar to amyotrophic lateral sclerosis [2]. The large multicenter studies reported that motor neuron dysfunction is the most frequent

Abbreviations: Spinocerebellar ataxias, SCA; motor neuron disease, MND; Electromyography, EMG; magnetic resonance imaging, MRI; computed tomography, CT; C-terminal Klarsicht/ANC-1/Syne homolog, KASH

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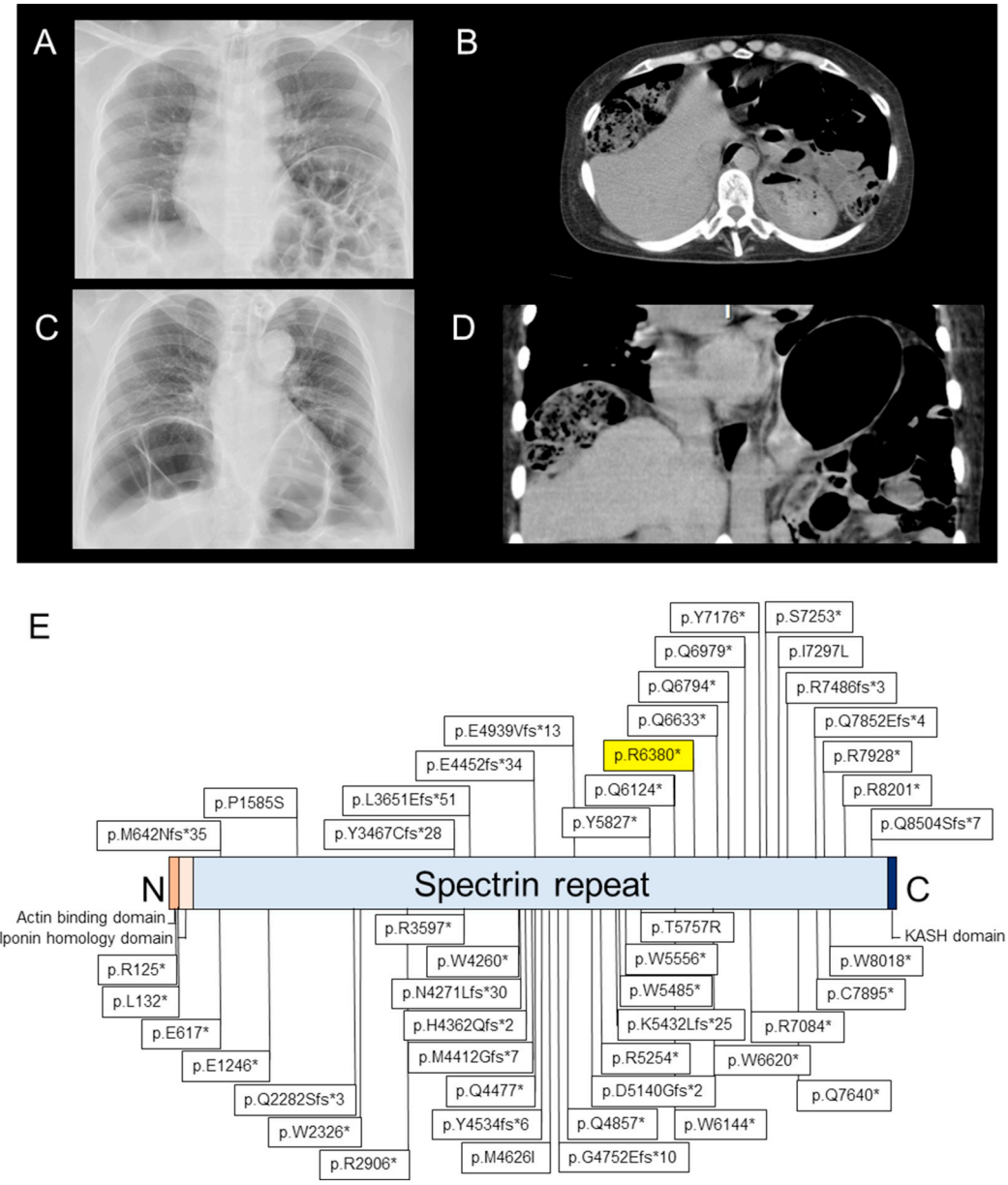

Fig. 1. Chilaiditi syndrome findings and previously reported mutations in *SYNE1*.
Chest radiograph (A) and abdominal CT (B,D) of the proband. Chest radiograph of the proband's sister (C). (D) Nesprin-1 and the location of previously reported variants are illustrated. The variants associated with motor neuron disease complications are shown in the upper part. The variants associated with relatively pure cerebellar ataxia with or without upper motor neuron signs are represented in the lower part. The variant identified in this study is marked in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

complication of SCAR8, observed in 58% of patients [3].

The Fig. 1E shows the locations of the previously reported variants in *SYNE1* [1–8]. The variants associated with MND tend to located in the C-terminal region compared to the variants associated with relative pure cerebellar ataxia. Similarly, the variant in our patients was located in the relative C-terminal region.

The *SYNE1* gene encodes a nesprin-1 protein, which is an intracellular linker and scaffolding protein containing an N-terminal actin-binding domain and C-terminal Klarsicht/ANC-1/Syne homolog (KASH)-domain. The short isoforms lacking the actin-binding domain are known as transcript variants of the full-length nesprin-1, which is called nesprin-1 giant. In the brain, nesprin-1 giant is the main transcript, and there are fewer transcripts of the short isoforms; however, some of the short isoforms containing the KASH-domain are expressed in muscle [9]. It was previously reported that the KASH-domain of nesprin-1 plays a crucial role in anchoring myonuclei and proper motor neuron innervation [10]. This report showed that Syne-1and Syne-2 KASH-domain double knockout mice died of respiratory failure due to impairment of phrenic nerve innervation. Because the short isoforms of nesprin-1 start at the 5406th, 7030th and 7728th methionines of nesprin-1 giant (NM_033071), mutations located in regions lower than these sites on the C-terminal could affect the expression of the short isoforms. In our cases and previsouly reported cases, significantly more mutations causing MND were located in regions lower than the 5406th methionine (MND and cerebellar ataxia group were respectively 14/20 [70%] and 10/27 [37%]; chi-square test $p = .025$). Collectively, nonsense mutations in the C-terminal region of *SYNE1* could cause lower motor neuron signs, abolishing the short isoforms containing the KASH-domain, which are important for motor neuron innervation.

Our patients had Chilaiditi syndrome which is a rare condition of

hepatodiaphragmatic interposition of the intestine predisposed by increased colonic mobility, reduced liver volume, a lax suspensory ligament, phrenic nerve palsy and obesity [11]. Although phrenic nerve palsy caused by MND could be a risk factor for Chilaiditi syndrome in our patients, diaphragmatic paralysis and malrotation of the colon were reported in patients with SCAR8 [3,4]. Chilaiditi syndrome might be one of the phenotypes of *SYNE1* mutations. We speculate that *SYNE1* mutation in the C-terminal might abolish the short isoforms of nesprin-1 in muscle and cause diaphragm muscle impairment as well as motor neuron dysfunction, resulting in Chilaiditi syndrome.

In conclusion, we reported a novel nonsense mutation of *SYNE1*, p.R6380*, causing SCAR8 associated with MND. Mutations in the C-terminal region of *SYNE1* could be associated with lower motor neuron signs, affecting the expression of the short isoforms of nesprin-1.

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