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【 CASE REPORT 】

Two Cases of Autosomal Recessive Spinocerebellar Ataxia-8 Showing Two Novel Variants of *SYNE1* in Japanese Families

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Abstract:

Autosomal recessive spinocerebellar ataxia-8 (SCAR8) is a neurodegenerative disorder caused by the biallelic pathogenic variants of *SYNE1*. It is characterized by slowly progressive cerebellar ataxia and atrophy. We identified two SCAR8 families using exome analyses and two novel variants, c.2127delG (p.Met709Ilefs) and c.15943G>T (p.Gly5315*), in *SYNE1* (NM_182961.4). Pathogenic variants of *SYNE1* cause various symptoms, including cerebellar ataxia, pyramidal tract disorders, and joint disorders, and the pathogenic variants discovered in this study were located in a region prone to cerebellar ataxia.

Key words: SCAR8, SCAR, cerebellar ataxia, whole-exome sequencing analysis

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Introduction

Spinocerebellar degeneration is a neurodegenerative disease characterized by progressive cerebellar ataxia and atrophy. Spinocerebellar degeneration predominantly follows an autosomal dominant mode of inheritance, referred to as spinocerebellar ataxias (SCAs), and includes multiple types of repeat expansion disorders. In particular, Machado-Joseph disease / SCA 3, SCA 6, SCA 31, and dentatorubral-pallidoluysian atrophy are common in Japan (1). Other inherited spinocerebellar degenerations include non-repeat expansion SCAs and autosomal recessive spinocerebellar ataxia (SCAR). Autosomal recessive spinocerebellar ataxia-8 (SCAR8) is a type of SCAR caused by biallelic pathogenic variants of *SYNE1* that was originally identified in Quebec, Canada (2). With advances in exome analysis methods, SCAR8 has increasingly been reported worldwide. Pathogenic variants of *SYNE1* have been reported to cause cerebellar ataxia, pyramidal tract signs, joint disorders, cognitive dysfunction, muscular dystrophy, and various other symptoms (3). However, the prevalence and phenotypic spectrum of SCAR8 variants in Japan remains largely unknown. We herein present two new families with SCAR8, and report two novel variants of *SYNE1*.

Methods

Prior to the genetic analysis, written informed consent was obtained from all participants after approval of the study by the Ethics Committee of Okayama University.

Genomic DNA was extracted from the peripheral blood leukocytes. Exome sequencing of the index patients was conducted using an Illumina platform with either the SureSelect V6 kit (Agilent) or Twist exome 2.0 (Twist Bioscience). Short reads were aligned to the human reference genome (hg38) using bwa-mem2 v2.2.1 (4). Aligned reads were further processed and variant calling was performed following the GATK Best Practices workflow (v4.3.0). Variant annotations were performed using the ANNOVAR software program (5). Rare variants were defined as those with a minor allele frequency (MAF) of <0.005 in all populations in the gnomAD database.

Variants in *SYNE1* were confirmed by direct nucleotide sequencing using the following primers: for patient 1, 5'-GCAGTCACCGGTTACAAGAA-3' and 5'-GGTCTGCCCAGTTCTCTGC-3' (6); patient 2 and family members: 5'-TGGAATGATTCTCGTTTCAAATCA-3,' 5'-TCTGACAGGTGCAAATTGGGA-3,' 5'-AGTGGCATGTGAGACAGTCA-3,' and 5'-TGGGTAAAGAGAATGAGGAGACTT-3.'

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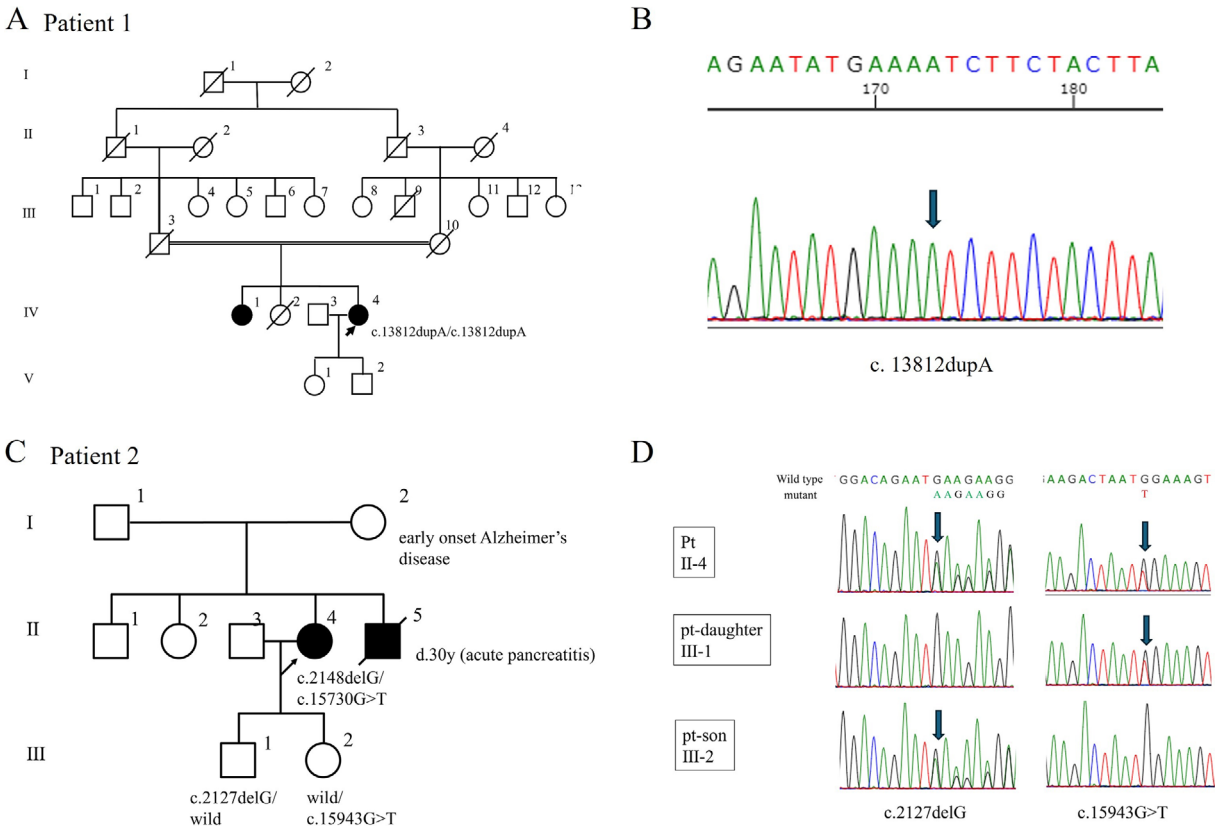

Figure 1. **Family tree and Sanger sequencing results of pathogenic variants. The parents of Patient 1 were cousins. The sister of the proband (IV-1) presented with similar signs and symptoms but declined to participate in the study (A). A direct nucleotide sequence analysis revealed a homozygous c.13812dupA (p.Tyr4605Ilefs) variant of *SYNE1* (NM_182961.4) (B). The parents of Patient 2 were not consanguineous (C). A direct nucleotide sequence analysis revealed the presence of compound heterozygous variants c.2127delG (p.Met709Ilefs) and c.15943G>T (p.Gly5315*) in *SYNE1* because her son and daughter possessed only one variant (D).**

Case Report

Patient 1

The patient was a 73-year-old woman. At 48 years of age, while standing on a chair and rearranging shelves, she fell and broke a bone. At that time, the patient wobbled during her gait. At 57 years of age, she fell and fractured her right femur. Since then, she required a cane to walk. She was admitted to our hospital at 58 years of age. Her parents were married to a cousin. The patient's sister also exhibited similar symptoms (Fig. 1A). A neurological examination revealed cerebellar ataxia, saccadic pursuit, scanning speech, dysmetria, dysdiadochokinesia, and a wide-based gait. Her cranial nerve examination results were normal. Her Mini-Mental State Examination (MMSE) score was 30. Muscle weakness, hyperreflexia, and pathological reflexes were observed. The results of nerve conduction studies, electromyography, and electroencephalography were normal. Brain magnetic resonance imaging (MRI) revealed atrophy of the cerebellar hemispheres and vermis. Mild atrophy of the superior cerebellar peduncle and the pons was suspected. ^{99}mTc-ethyl cysteinate dimer (ECD) single-photon emission computed tomography (SPECT) revealed decreased blood flow confined to the cerebellum (Fig. 2A). The patient was diagnosed with SCAR because her parents were consanguineous.

We performed whole-exome sequencing and identified a homozygous variant, c.13812dupA (p.Tyr4605Ilefs), in *SYNE1* (NM_182961.4) (Fig. 1B). SCAR8 was diagnosed on based on the presence of the same homozygous variant previously reported in a patient with pure cerebellar ataxia (6).

Patient 2

The patient was a 53-year-old woman who presented with dysarthria in her teenage years. At 31 years of age, she visited a hospital for headache and underwent computed tomography, which revealed cerebellar atrophy. She became wobbly and dysarthric at 35 years of age. She was admitted to our hospital at 42 years of age. The parents of the patient were not consanguineous. The patient's brother exhibited similar symptoms (Fig. 1C). A neurological examination revealed cerebellar ataxia, saccadic pursuit, scanning speech, dysphagia when drinking liquids, dysmetria, dysdiadochoki-

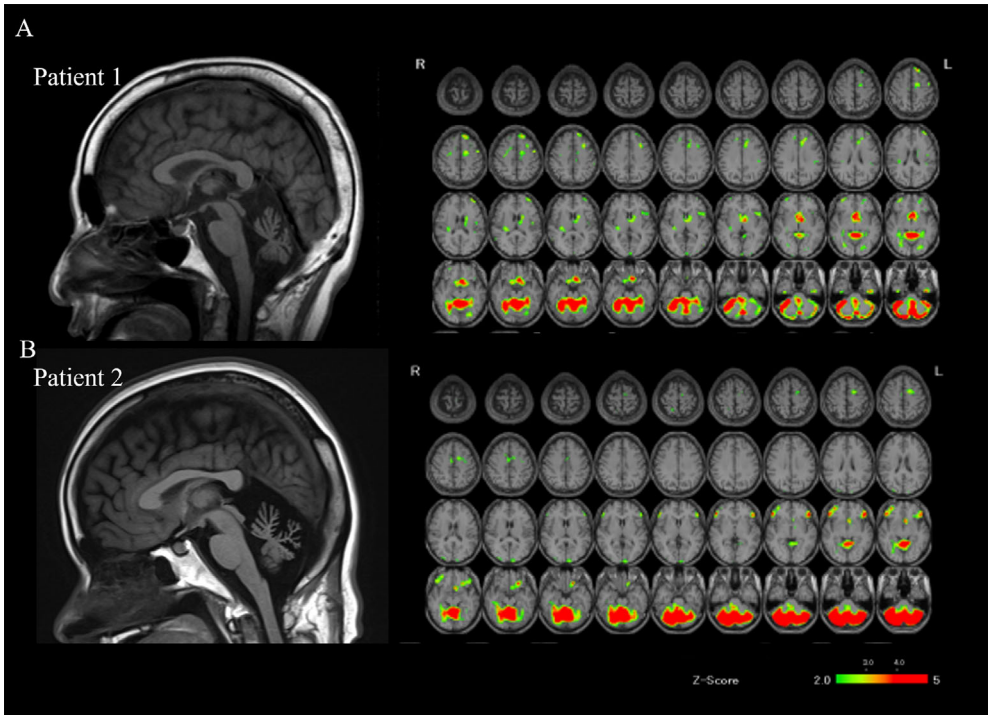

Figure 2. Brain MRI and ^{99m}Tc-ECD SPECT. T1-weighted images indicating atrophy in the cerebellar hemispheres and cerebellar vermis in patient 1 at 64 years of age (A) and in patient 2 at the 42 years of age (B). eZIS analyses using ^{99m}Tc-ECD SPECT revealed reduced cerebellar blood flow in both of the patients. eZIS: Easy Z-score imaging system, ECD: ethyl cysteinate dimer, MRI: magnetic resonance imaging, SPECT: single-photon emission computed tomography

nesia, and a wide-based gait. Her cranial nerve examination results were normal. Her MMSE score was 30. The patient did not exhibit any muscle weakness. She had a hyperactive patellar tendon reflex and positive Babinski reflex on the right side. The results of nerve conduction studies, electromyography, and electroencephalography were normal. Brain MRI revealed atrophy of the cerebellar hemispheres and vermis without atrophy of the pons or peduncles. ^{99m}Tc-ECD SPECT revealed decreased blood flow confined to the cerebellum (Fig. 2B). The patient was diagnosed with hereditary spinocerebellar degeneration. She has been followed-up on an outpatient basis for 10 years, with very slow progression.

A whole-exome analysis identified the variants c.2127 delG (p.Met709Ilefs) and c.15943G>T (p.Gly5315*) in *SYNE1* (NM_182961.4), as confirmed by a direct nucleotide sequence analysis (Fig. 1D). Her son and daughter were genetically tested and the results indicated compound heterozygous variants in the patient. Both variants were predicted to be loss-of-function variants and we concluded that they were pathogenic.

Discussion

SCAR8 is a type of SCAR caused by biallelic pathogenic variants of *SYNE1*. It is characterized by slowly progressive cerebellar ataxia and atrophy. The age of disease onset ranged from 17 to 46 years (7). Most patients exhibit pure cerebellar ataxia, whereas approximately one-fourth of the patients with SCAR8 present with hyperreflexia or pyramidal signs in their legs. These findings are consistent with the clinical features observed in these two patients.

We identified one known variant and two novel variants, c.2127delG and c.15943G>T, in *SYNE1* (NM_182961.4). These variants have not been described in the Human Gene Mutation Database or in ClinVar. Loss-of-function variants were consistent with disease causation. The c.2127delG variant has not been previously described in jMorp or gnomAD patients. The c.15943G>T variant was absent in jMorp, but was described in gnomAD (allele frequency is 0.00002230 in East Asia and has not been reported in other regions).

SYNE1 is a large gene composed of 146 exons encoding nesprin-1, a protein of 8,797 amino acids. Biallelic loss-of-function variants of *SYNE1* are associated with ataxia and motor neuron disease. Pathogenic variants closer to the N-terminus tend to present with a pure cerebellar form, whereas those closer to the C-terminus present various symptoms (3). All three variants identified in this study were located at either the N-terminus or middle region of nesprin-1. The patient exhibited pure cerebellar ataxia or pure cerebellar ataxia with hyperreflexia. This finding, along with the distribution of the pathogenic variants from the N-terminus to the middle region, is consistent with previous reports (3). In contrast, heterozygous missense variants in *SYNE1* cause Emery-Dreifuss muscular dystrophy 4, whereas biallelic truncating variants in the C-terminus of SYNE1 cause arthrogryposis multiplex congenita 3, a myogenic type.

Nesprin-1 exists in numerous isoforms that are produced via alternative splicing. The largest isoform, nesprin-1 giant (Nes1 g), is specifically expressed in the central nervous system. Klarsicht/ANC-1/Syne homology (KASH)-less nesprin-1 giant (KLNes1 g), which lacks the C-terminal KASH domain of Nes1 g, is strongly expressed in mossy fiber glomeruli. Therefore, truncating variants in the N-terminus to the middle region of *SYNE1* affects the expression of Nes1 g and KLNes1 g, both of which are thought to be associated with the ataxic phenotype, but do not affect the C-terminal dominant isoforms of nesprin-1, in which transcription start sites are downstream of the middle region of *SYNE1*. These C-terminal dominant isoforms contain the KASH domain and are predominantly expressed in the skeletal muscle, which may explain why near-C-terminal variants of SYNE1 are associated with arthrogryposis or other phenotypes (3, 8, 9).

SCAR is rare in comparison to autosomal dominant SCAs. Relative to individuals of European descent, the Japanese population exhibits a distinctive distribution in the frequency of SCAR, with no reported cases of Friedreich's ataxia (10) and an extremely low prevalence of spastic paraplegia 7 (11, 12). Early-onset ataxia with oculomotor apraxia and hypoalbuminemia (EAOH/AOA1) caused by variants in *APTX* (13), autosomal recessive spinocerebellar ataxia with axonal neuropathy 2 (SCAN2) caused by variants in *SETX* (14-17), autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) caused by variants in *SACS* (18), and ataxia with vitamin E deficiency (AVED) caused by variants in *TTPA* (19, 20) have been frequently reported in Japan.

Together with the present report, 11 genetically confirmed individuals from nine SCAR8 families have been reported in Japan to date (6, 21-24). Of these, four families exhibited pure cerebellar ataxia, two exhibited hyperreflexia in conjunction with ataxia, and three experienced ataxia plus motor neuron disease. Few cases exhibit different phenotypes within a family, and there seems to be an association between the phenotypes and pathogenic variants.

In conclusion, we identified two SCAR8 families with pathogenic variants of *SYNE1*, two of which were novel. These cases exhibited a typical clinical presentation of SCAR8; however, we should be cautious as *SYNE1* variants may present with various symptoms. Furthermore, the actual frequency of SCAR8 remains unknown, and should be investigated in future studies. There is a need to search not only for patients with pure ataxia, but also for those with cerebellar ataxia plus phenotype and cerebellar ataxia associated with motor neuron disease.

The authors state that they have no Conflict of Interest (COI).

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Ethics statement

Ethical permission for this study was provided by the Ethics Committee on Epidemiological Studies of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and the participating hospital (approval #2109-031).

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