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Short communication

Exome sequencing reveals a novel *MRE11* mutation in a patient with progressive myoclonic ataxia

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ABSTRACT

Progressive myoclonic ataxia (PMA) is a clinical syndrome defined as progressive ataxia and myoclonus and infrequent seizures in the absence of progressive dementia. Due to the extremely heterogeneous nature of PMA, a large proportion of PMA cases remain molecularly undiagnosed. The aim of this study was to clarify the molecular etiology of PMA. The patient was a 52-year-old female from consanguineous parents. She developed a jerking neck movement at age 9, which gradually expanded to her entire body. On physical examination at age 47, she exhibited generalized, spontaneous myoclonus that occurred continuously. She also presented with mild limb and truncal ataxia. An electroencephalogram revealed no abnormalities. A brain MRI displayed no atrophy of the cerebellum. Electrophysiological studies suggested myoclonus of a subcortical origin. For further evaluation, we performed exome sequencing, and we identified a novel homozygous missense mutation in the *MRE11* gene (NM_005590:c.140C>T:p.A47V). Subsequently, we analyzed the expression of MRE11 and related proteins (RAD50 and NBS1) via Western blot, and they were markedly decreased compared to a healthy control. Mutations in the *MRE11* gene have been known to cause an ataxia–telangiectasia-like (ATLD) disorder. Accumulating evidence has indicated that its wide phenotypic variations in ATLD correspond to genotypic differences. Interestingly, our case exhibited a relatively mild decrease in NBS1 compared to previously reported cases of a homozygous missense mutation, which may account for the milder phenotype in this patient. Moreover, together with a recently reported case of an *MRE11* mutation, it is suggested that *MRE11* mutations can present as PMA.

1. Introduction

Progressive myoclonic ataxia (PMA) is a clinical syndrome defined as progressive ataxia and myoclonus with no or infrequent seizures in the absence of progressive dementia [1]. Known causes of PMA include various diseases characterized by distinct molecular etiologies [1]: Unverricht–Lundborg disease, caused by mutation in the cystatin B gene (*CSTB*) [2]; mitochondrial encephalomyopathy; sialidosis caused by mutation in the gene encoding neuraminidase (*NEU1*) [3]; Lafora body disease, caused by dysfunctions of a dual-specificity protein phosphatase (*EPM2A*) [4] or a single E3 ubiquitin ligase subunit (*NHLRC1*) [5]; neuronal ceroid lipofuscinosis, caused by the intracellular accumulation of autofluorescent lipopigment storage material [6]; and spinocerebellar degeneration. In the case series on PMA by Marsden et al., the authors emphasized the low diagnostic yields of PMA, and since the publication of the case series in 1990, no new specific etiology of classical PMA has been reported. One reasonable explanation for the difficulties in the etiological diagnosis of PMA could be that PMA consists of rare heterogeneous disorders that escape the conventional diagnostic approach.

In this report, due to advances in molecular diagnostic technologies, we performed exome sequencing of a PMA patient and identified a novel mutation in the MRE11 meiotic recombination 11 homolog A (*MRE11*) gene. Mutations in *MRE11* have been known to cause an ataxia–telangiectasia-like disorder (ATLD), which typically produces gradually progressive cerebellar ataxia and oculomotor apraxia but rarely exhibits tumors or immunodeficiency, as observed in ataxia–telangiectasia (AT) [7,8]. Although ATLD is a very rare disease and only a few

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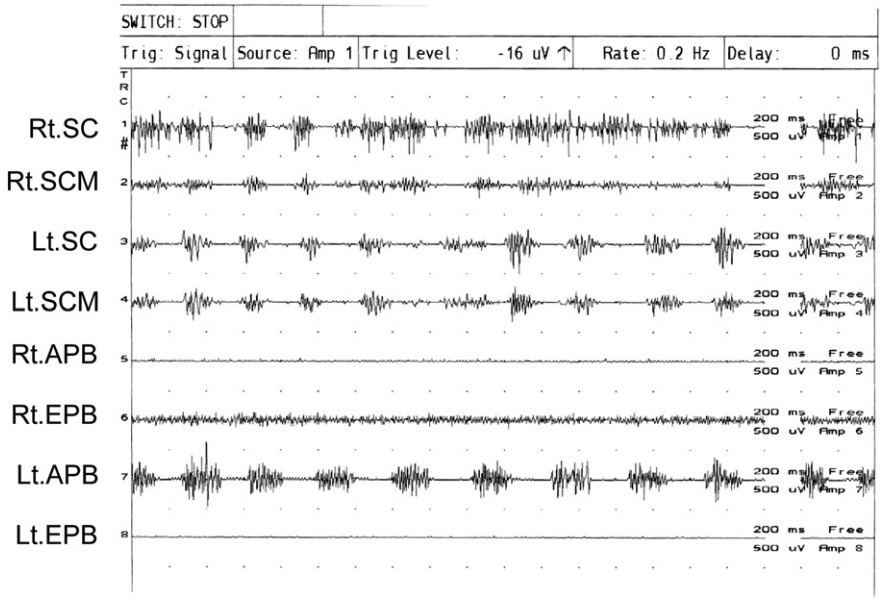

Fig. 1. Superficial EMG. Rhythmic bursts of approximately 3 Hz were observed in Lt.SC and Lt.SCM. In Rt.SC and Lt.APB, the burst duration was much longer, which suggested the co-existence of myoclonus and dystonia. These findings suggested that she experienced a combination of tremor, myoclonus, and dystonia. We placed an emphasis on myoclonus throughout this report due to the clinical phenomenology (see video). Abbreviations: SC = splenius capitis muscle; SCM = sternocleidomastoid muscle; APB = abductor pollicis brevis muscle; EPB = extensor pollicis brevis muscle; Rt = right; Lt = left.

mutations have been reported, increasing evidence has suggested that ATLD patients can present with different symptoms [8–10]. In this study, we describe the unique clinical characteristics of a patient with a novel homozygous *MRE11* mutation, and we discuss the genotype–phenotype correlation.

2. Methods

The study was approved by the ethics committee of Hiroshima University, and the patient provided written informed consent.

2.1. Patient

The patient was a 52-year-old Japanese female who was born to half cousin parents. Her mother and two siblings were in good health, and her father had a history of stroke due to a carotid artery occlusion. She grew normally until age 9, when she developed an intermittent jerking neck movement. She underwent an examination that included an EEG, but the results were normal. Three years later, she presented with myoclonus and a tremor in her right hand that was triggered by writing. Her myoclonus slowly expanded to her entire body, which forced her to leave her job as a dressmaker at age 21. The involuntary movement was refractory to the administration of clonazepam, L-3,4-dihydroxyphenylalanine, and benzodiazepines. She began to exhibit mild walking instabilities at approximately age 40.

She was referred to our hospital at age 47, while being able to take care of normal household tasks. On physical examination, she experienced upper body-dominant spontaneous myoclonus that occurred continuously and was exacerbated by fine movements or emotional stress. A startle response was not induced by touching or sound. She exhibited dysmetria based on the finger–nose–finger test and the heel–knee test, as well as dysdiadchokinesis based on the pronation–

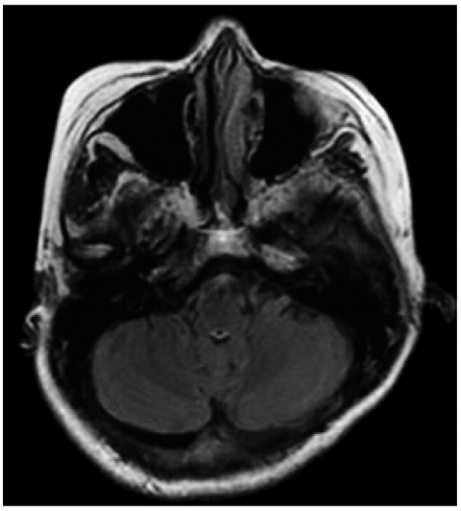

Fig. 2. Brain MRI at age 47 (FLAIR). The cerebellum was preserved.

Table 1
Sequence information and filtering criteria used to identify the mutation.

	Patient
Total reads	129,722,696
Total yield (bp)	12,972,269,600
Mappable reads	114,690,581
% mappable reads (out of total reads)	88.4
Mean read depth of target regions	116X
Filters applied	**Number of variants**
Total variants	80,852
Homozygous variants	37,439
Exonic/splicing variants	9581*
Not present in dbSNP135, 1000 genomes or ESP5400	57
Frameshift/nonsense/nonsynonymous variants	8
In identity by descent (IBD) regions (cut-off 3.0 cM)	5
Not present in 206 population-matched control alleles	4**
Predicted as damaging via >2 algorithms	1 (*MRE11*)

*Of the 9581 variants, 65 had rsIDs with a minor allele frequency <0.005. None of the 65 variants were included in the flagged SNPs or located in the genes known to cause ataxia or myoclonus. **Variants were identified in the following genes: *TRIM63*, *DDX4*, *IL6ST*, and *MRE11* (see Table 2). We verified that this patient did not harbor a novel or low-frequency (<0.005) heterozygous/homozygous variant in the *MRE11*, *NBS1*, or *RAD50* genes except for the identified mutation in *MRE11*. Additionally, we have searched for mutations in the genes that have been known to cause a PMA phenotype: *CSTB* (Unverricht–Lundborg disease), *NEU1* (sialidosis), *EPM2A*, *NHLRC1* (Lafora body disease), *PPT1*, *TPP1*, *CLN3*, *CLN6*, *DNAJC5*, *CLN5*, *CLN6*, *MFSD8*, *CLN8*, *CTSD*, and *GRN* (neuronal ceroid lipofuscinosis). None of these genes harbored possible causative variants.

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