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Short communication

Prevalence and clinicoradiological features of spinocerebellar ataxia type 34 in a Japanese ataxia cohort

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ABSTRACT

Introduction: Spinocerebellar ataxia (SCA) type 34, a form of autosomal dominantly inherited ataxia, has recently been associated with mutations in the *ELOVL4* gene. However, a genetic study of the prevalence of SCA34 in an ataxia cohort has never been reported.

Methods: We performed a mutation screening of *ELOVL4* in a cohort of 153 undiagnosed index ataxia patients, selected after excluding for common SCA types, in a series of 506 Japanese index ataxia patients.

Results: Heterozygous mutation c.698C > T (p.T233M) was detected in an index patient with multisystem neurodegeneration including ataxia and erythrokeratodermia skin lesions, an archetypal skin phenotype in SCA34. The patient's father also presented with ataxia but not skin lesions. Although this mutation has been recently reported in a single English–Canadian patient, the present study confirms its cosegregation with the ataxia phenotype in the Japanese kindred. Brain magnetic resonance imaging (MRI) of the patient and his father revealed marked pontine and cerebellar atrophy as well as the hot cross bun sign, that is common in cerebellar type of multiple system atrophy and was also described in SCA34 patients harboring two other mutations: p.L168F and p.W246G.

Conclusion: This represents the first genetic study of the prevalence of SCA34 in an ataxia cohort and demonstrates its low prevalence (0.2%) in ataxia patients. The broad SCA34 clinical spectrum suggests variable multisystem neurodegeneration. Clinicians should be aware of this rare disease entity, particularly if erythrokeratodermia or the hot cross bun sign in MRI are present in undiagnosed degenerative ataxia patients.

1. Introduction

Spinocerebellar ataxias (SCAs) are autosomal dominant neurodegenerative disorders displaying ataxia and various neurological symptoms. An increasing number of SCA subtypes, currently identified as SCA 1 to 48, have been reported, with many of their causative mutations already identified. Among them, several missense mutations in *ELOVL4* and *ELOVL5* genes, which encode very long-chain fatty acid elongases, have recently been reported to cause SCA34 and SCA38 phenotypes, respectively [1–5].

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ELOVL4 encodes a 314 amino acid-protein designated elongation of very long-chain fatty acids protein 4 (ELOVL4), which is expressed in the brain, retina, skin, and testis [6] and mainly localized in the endoplasmic reticulum (ER) membrane. ELOVL4 protein is involved in the elongation of C26-C28 or longer fatty acids, which are used for the biosynthesis of lipid substances, such as cholesterol esters, ceramides, phosphatidylcholine, and sphingomyelin [6].

The SCA34 phenotype was originally reported in a large French–Canadian kindred harboring a heterozygous c.504G > C (p.L168F) *ELOVL4* mutation, which exhibited cerebellar ataxia with a type of skin lesion called erythrokeratodermia (EK). However, two Japanese families harboring a c.736T > G (p.W246G) mutation showed no apparent signs of EK [1,2]. Two other *ELOVL4* mutations, c.539A > C (p.Q180P) and c.698C > T (p.T233M), described in single South American and English–Canadian patients, respectively, have been associated with SCA with EK [5,7]. While French–Canadian, Japanese, South American, and English–Canadian patients were independently studied and identified as having SCA34, no genetic study of disease prevalence in an ataxia cohort has, to the best of our knowledge, been reported to date.

This study reports, for the first time, mutation screening in 153 undiagnosed degenerative ataxia patients negative for common SCAs, such as SCA1, 2, 3/Machado–Joseph Disease, 6, 31, and dentatorubral–pallidoluysian atrophy (DRPLA), in a series of 506 Japanese ataxia patients. The heterozygous c.698C > T (p.T233M) mutation, recently reported in a single patient of English–Canadian origin [7], was detected in a two-generation Japanese kindred with progressive ataxia, together with various neurological signs suggestive of multisystem neurodegeneration. Skin lesions compatible with EK were found on the proband, and brain magnetic resonance imaging (MRI) of the proband and his father revealed not only cerebellar and pontine atrophy but also the hot cross bun sign in the pons, a feature previously reported in our study of SCA34 patients with p.W246G mutation and in association with the original p.L168F mutation [8].

2. Subjects and methods

2.1. Subjects and sample preparation

A series of 506 unrelated index patients diagnosed by board-certified neurologists in Tokyo Medical and Dental University Hospital or associated hospitals as having degenerative cerebellar ataxia without autoimmune, infectious, metabolic, toxic, cerebrovascular, or paraneoplastic causes was investigated and genetically diagnosed at the Department of Neurology and Neurological Science in Tokyo Medical and Dental University between January 2010 and December 2017. Of the 506 patients studied, 153 tested negative for common SCAs such as SCA1, 2, 3/Machado–Joseph Disease, 6, 31, and DRPLA, and were classified as “unidentified”. A family history of SCA within at least third degree of the index patient was considered to suggest a familial case. Patients who met the clinical criteria for possible or probable multiple system atrophy (MSA) were excluded from the study [9]. This study was approved by the local ethics committee of Tokyo Medical and Dental University. After retrieving patients’ written informed consent, in accordance with the Declaration of Helsinki, blood samples were collected, and genomic DNA was extracted using standard protocols.

2.2. Genetic analysis

For *ELOVL4* mutation screening (Refseq NM_022726), all coding sequences and exon–intron boundaries were amplified by polymerase chain reaction (PCR) using primers described in supplement eTable 1. PCR amplified fragments were sequenced using the BigDye 3.1 system (Thermo Fisher Scientific, Waltham, MA, USA) and characterized using a 3130xl genetic analyzer (Applied BioSystems, Foster City, CA, USA).

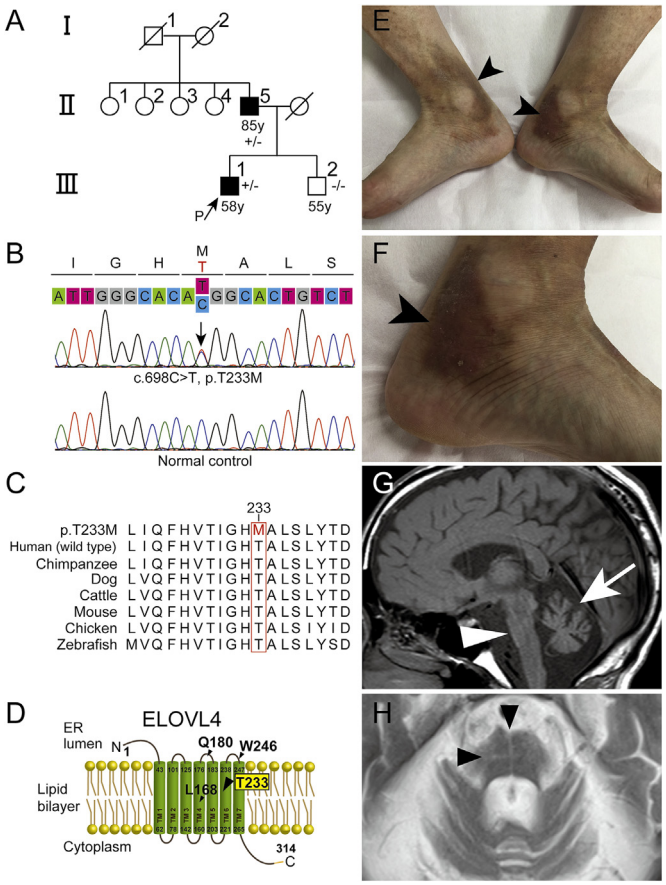

Fig. 1. A Japanese SCA family with mutation (p.T233M) in *ELOVL4*. A, Pedigree of a Japanese family with spinocerebellar ataxia (SCA) caused by the p.T233M mutation in *ELOVL4*. Arrow indicates the proband in the family. Squares indicate male, and circles indicate female; black-filled symbols indicate family members with ataxia; diagonal lines indicate deceased members; +/− indicates heterozygous for the mutation; −/− indicates homozygous for wild-type allele. III-1 had skin lesions compatible with erythrokeratodermia (EK), as shown in E and F. B, Electropherograms around 698th nucleotide of the proband (III-1) harboring mutation c.698C > T, p.T233M in *ELOVL4* (arrow in the upper electropherogram) and unaffected individual without mutation (lower electropherogram) (III-2) aligned with the corresponding amino acid sequence. Mutation was detected in affected individuals (II-5 and III-1 in A). C, ELOVL4 amino acid sequence alignment among species. The affected amino acid threonine 233 residue (red rectangles) in p.T233M mutation is highly conserved from zebrafish to human. D, Schematic diagram of ELOVL4 protein (in green) showing the recognized mutational sites (p.L168F, p.Q180P, p.T233M, and p.W246G) leading to SCA34 with the topological prediction of ELOVL4 protein, based on the calculation by MEMSAT-SVM [1]. Threonine 233 is located on the sixth transmembrane alpha helical segment. Yellow carboxy-terminus in the protein shows endoplasmic reticulum (ER)-retention signal sequence. TM, transmembrane alpha helix; N, amino-terminus; C, carboxy-terminus. E and F, Images of the proband (III-1) ankles showing skin lesions compatible with EK. Demarcated brown erythematous areas with hyperkeratosis were observed (arrowheads). G and H, MRI of the two affected individuals [III-1 (proband; G) and II-5 (his father; H)]. G, Sagittal T1 weighted image of the proband (III-1) showed marked atrophy in the pontine base (arrowhead) and cerebellum (arrow). H, The hot cross bun sign (arrowheads) and atrophy in the basis pontis and cerebellum were observed in II-5. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3. Functional prediction of ELOVL4 mutations with bioinformatics tools

To predict the pathogenicity of p.T233M mutation, bioinformatics tools polyphen-2, SIFT, and PROVEAN were used as described [1]. In addition, because ELOVL4 is a multipass transmembrane protein

located at the ER membrane, MEMSAT-SVM was used to predict transmembrane alpha-helices and the orientations of amino and carboxy termini [1].

3. Results

3.1. Mutation screening of ELOVL4 in Japanese population

In total, 153 (88 male, 64 female, one gender-undisclosed) unidentified index patients with degenerative cerebellar ataxia (see details in supplement eTable 2) were studied. Mutation screening of *ELOVL4* revealed a heterozygous mutation c.698C > T (p.T233M) in one (0.7%) index patient (Fig. 1-B), but no mutations in the other 152 patients (supplement eText 1). This mutation had been recently reported in a single English–Canadian patient with SCA34 [7]. The threonine 233 of ELOVL4 protein, which is changed in p.T233M mutation, is well conserved among species going from zebrafish to humans (Fig. 1-C). Three bioinformatics functional prediction tools suggested the detrimental nature of this mutation (supplement eText 2). As reported in our previous study [1], the topology prediction tool MEMSAT-SVM suggested seven transmembrane helices in ELOVL4 protein and threonine 233 in the sixth transmembrane region (Fig. 1-D).

3.2. Detailed description of a kindred with c.698C > T (p.T233M) mutation

Patient's kindred with c.698C > T (p.T233M) mutation was subsequently analyzed. The kindred harbored two progressively ataxic patients, the proband (III-1, a 58 year-old man) and his father (II-5, an 85 year-old man) (Fig. 1-A). The two patients were subjected to detailed neurological examination and brain MRI evaluation and investigated for past and current history of erythrokeratodermia (EK) (supplement eTable 3).

3.3. Clinical characteristics of the proband (III-1 in Fig. 1-A)

The 58 year-old man presented with slowly progressive gait ataxia since the age of 39 years (see details in supplement eTable 3). On neurological examination, he displayed moderate ophthalmoplegia on upward gaze, saccadic eye movement, nystagmus, and mild dysarthria. Spasticity in lower limbs, pyramidal tract signs, and mild hypokinesia were noted. Mild decrease in vibration sense was observed in distal lower limbs. He showed limb ataxia more prominently in the lower limbs than in the upper limbs, as well as marked truncal ataxia. Skin lesions comprising demarcated erythematous keratotic areas compatible with EK were present in bilateral ankles (Fig. 1-E and 1-F) for 3 years, with the subject denying the presence of skin lesions during youth. The subject's visual acuity with glasses was normal in both eyes when he was 57 years old; however, we did not conduct detailed ophthalmological evaluations such as fundoscopy or electroretinogram. Brain MRI showed atrophy in cerebellum and basis pontis (Fig. 1-G). Of note, a pontine hot cross bun sign on T2-weighted images was observed (see supplement eFig. 1-A and its legend).

3.4. Clinical characteristics of patient II-5 (Fig. 1-A)

The 85 year-old man, father of the proband (III-1), presented with slowly progressive gait ataxia in his sixth decade of life (see details in supplement eTable 3). On examination, he showed cognitive disturbances, vertical ophthalmoplegia prominent in the upward gaze, very saccadic eye movement, nystagmus, and dysarthria. Spasticity in the lower limbs and mild cogwheel rigidity in the left upper limb were observed. Pyramidal tract signs and mild hypokinesia were also observed. He showed mildly decreased vibration sense in the distal lower limbs. Marked ataxia was seen in the trunk and shown to be dominant in the lower limbs. Physical examination and research of the medical records revealed no evidence of EK. Overt vision loss was not reported; however, a detailed ophthalmological evaluation was not conducted. Brain MRI showed remarkable atrophy in basis pontis as well as cerebellum (Fig. 1-H). Brain MRI also notably showed the hot cross bun sign on T2-weighted images (Fig. 1-H). Atrophy in frontal, temporal, and parietal lobes, as well as midbrain was observed (supplement eFig. 1-C, 1-D, and 1-E). The heterozygous mutation c.698C > T (p.T233M) was confirmed in II-5.

Additionally, a 55 year-old younger brother of III-1 (III-2), healthy and with no neurological symptoms, EK, or visual symptoms, was negative for c.698C > T (p.T233M) mutation. Cosegregation of the mutation and disease was thus confirmed in this small kindred.

4. Discussion

This is the first genetic study of the prevalence of SCA34 in patients with unidentified degenerative cerebellar ataxia. It revealed the low prevalence of SCA34, which occurred in 0.7% of 153 unidentified degenerative ataxia index patients and in 0.2% of a series of 506 Japanese index patients including major SCA types. An *ELOVL4* mutation (p.T233M) was further identified in a Japanese kindred and its clinical and radiological details were described. Overall, the present study together with the previous report of a single English–Canadian case [7], strongly suggests that p.T233M is a causative mutation of SCA34, by providing evidence of mutation and phenotype cosegregation. The mutation affected the evolutionarily well-conserved amino acid residue and was predicted to damage protein function.

The clinical characteristics of the two Japanese cases and English–Canadian case with p.T233M mutation are fundamentally similar in the slowly progressive course of gait ataxia, EK, and pontine base and cerebellar atrophy in brain MRI (eTable 3). However, several differences were detected in neurological findings, including neuro-ophthalmic features and pyramidal tract signs (eTable 3). Also, when compared with cases of SCA34 with known mutations (Table 1), pyramidal tract signs were observed in the Japanese subjects with p.T233M and p.W246G mutations but not in the English–Canadian case or in cases with p.L168F and p.Q180P mutations. Considering that hyporeflexia has been reported not only in the English–Canadian case with p.T233M but also in the original kindred with p.L168F mutation (Table 1) and that mildly reduced vibration sense was also observed in both patients in the current study, it is possible that peripheral neuropathy or posterior column involvement along with pyramidal tract signs are features of SCA34.

Cognitive decline and cortical atrophy observed in one of this study's patients (II-5) may be derived from incidental co-occurrence of a common neurological disease, such as Alzheimer's disease, or may also represent another feature of SCA34, particularly in view of the recently reported neuropsychiatric disturbances in patients with p.L168F (Table 1) [8]. Additionally, mild hypokinesia was observed in the two patients with p.T233M mutation. Overall, this pool of data suggests that SCA34 clinical features may be characterized by ataxia and skin lesions along with variable multisystem neurodegeneration that includes neuropsychiatric disturbances, dementia, neuro-ophthalmic signs, pyramidal tract signs, and perhaps extrapyramidal tract signs, and autonomic disturbances (Table 1).

The hot cross bun sign was observed in brain MRI of both patients with p.T233M, in addition to marked pontine base and cerebellar atrophy. The hot cross bun sign and its preceding form, pontine midline linear hyperintensity, have been originally characterized in cerebellar type of MSA (MSA-c) patients [10] and were also described in SCA1, 2, Machado–Joseph disease/SCA3, 7, 8, 17, DRPLA, SCA34, and other forms of the disease [1,11,12]. In addition to the SCA34 patients with the p.W246G mutation, the hot cross bun sign was also reported in patients with the p.L168F mutation who underwent MRI (Table 1) [8]. Together with EK, it can be a clue toward disease diagnosis in unidentified degenerative ataxia patients, particularly when EK history is

Table 1
Comparison of clinical characteristics among SCA34 patients with four heterozygous mutations in *ELOVL4*.

Study	Cadieux-Dion et al. [2], Beaudin et al. [8]	Bourassa et al. [5]	Bourque et al. [7], Ozaki et al. (this study)	Ozaki et al. [1]
Mutation	c.504G > C, p.L168F	c.539A > C, p.Q180P	c.698C > T, p.T233M	c.736T > G, p.W246G
Ethnicity	French–Canadian	South–American	English–Canadian and Japanese (this study)	Japanese
Pedigree/case (total number of patients studied)	Pedigree (19 mutation carriers)	Single case (1 patient)	Single case and pedigree (3 patients)	Two pedigrees (9 patients)
Onset	Avg. 51 years	Mid-20s	15–50s	Avg. 33.9 years
Characteristic neurological findings (inclusive)	Cognitive dysfunction (executive function and visuospatial skills) and psychiatric features, nystagmus, slow pursuit, limb and truncal ataxia, and decreased tendon reflex	Nystagmus, mild bilateral ophthalmoplegia, dysarthria, limb and truncal ataxia, normal deep tendon reflex	Dementia, neuro-ophthalmic findings including nystagmus and vertical ophthalmoplegia, dysarthria, limb and truncal ataxia, pyramidal tract signs or reduced deep tendon reflex, extrapyramidal signs, and mildly reduced vibration sense	Ophthalmoplegia (vertical > horizontal), nystagmus, limb and truncal ataxia, pyramidal tract signs, bladder and bowel disturbances
EK	14 of 19 cases with EK	One case with EK	2 of 3 cases with EK	None of 9 cases with EK
Brain MRI	Atrophy in basis pontis and cerebellum. Hot cross bun sign in 2 of 9 cases.	Atrophy in pons and cerebellum.	Atrophy in basis pontis and cerebellum, as well as in cerebral cortex. Hot cross bun sign in 2 of 3 cases.	Atrophy in basis pontis and cerebellum. Hot cross bun sign in 4 of 6 cases and PMH in 2 of 6 cases.

EK: Erythrokeratodermia; PMH: pontine midline hyperintensity.

obscure.

Although the present study estimated SCA34 prevalence and broadened its clinical spectrum, it has the limitation that only a Japanese population was analyzed. This study also shows selection bias for patients from Eastern Japan, due to the location of our facility. Therefore, this topic warrants a more comprehensive nation-wide study in the future. Further SCA34 investigation should include other ethnic backgrounds, such as other Asian, African, and Caucasian populations.

5. Conclusions

This study reports the first genetic study of the prevalence of *ELOVL4* mutations in 153 unidentified SCA patients in Japan, with results suggesting that SCA34 is a very rare entity. A small kindred with SCA34 harboring p.T233M mutation was identified. Combined data from current and previous studies on SCA34 suggest that ataxia plus EK and multisystem neurodegeneration can be distinguishing features of this condition. Clinicians should be aware of this rare disease entity, particularly if skin lesions or the hot cross bun sign in MRI are present in unidentified SCA patients.

Author contributions.

Planning, P; Clinical study, C; Collecting DNA samples, D; Sequencing and analysis of data, A; Drafting, W; Revising manuscript, R; Supervising the study, S.

KO: PCDAWR.
AA: A.
KN, TA, TK: C.
TI, MH, NS, KS: D.
HM: DRS.
KI: CDRS.
TY: S.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.019.

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