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Short communication

Identification of a new homozygous frameshift insertion mutation in the SIL1 gene in 3 Japanese patients with Marinesco–Sjögren syndrome

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Abstract

Marinesco–Sjögren syndrome (MSS) is an autosomal recessive multisystem disorder characterized by cerebellar ataxia, cataracts, progressive muscular weakness, and developmental and mental retardation. Recently, mutations in the SIL1 gene on chromosome 5q31 have been shown to be a cause of MSS. We sequenced the entire SIL1-coding region in 3 unrelated Japanese patients with classical MSS and identified a novel homozygous frameshift insertion mutation, 936_937insG, in exon 9 in all 3 patients.

Keywords: Marinesco–Sjögren syndrome; SIL1 gene; Mutation; Autosomal recessive disease; Cerebellar atrophy; Mental retardation; Cataract; Loss-of-function

1. Introduction

Marinesco–Sjögren syndrome (MSS) is a rare autosomal recessive multisystem disorder. The cardinal features of MSS are cerebellar ataxia, cataracts, short stature, and mental retardation [1–3], though it may also be present with hypergonadotrophic hypogonadism, skeletal abnormalities, dysmorphism, epilepsy, progressive myopathy, or neuropathy [1–3]. Recently, mutations in the SIL1 gene on chromosome 5q31 have been shown to cause MSS [4–7]. However, MSS is considered a clinically and genetically heterogeneous disorder, since SIL1 gene mutations are not always found in patients with classical MSS [5] and have been found in no patients with atypical MSS [5,8]. We therefore sequenced all 10 exons of the SIL1 gene in 3 unrelated Japanese patients with classical MSS, and identified a new frameshift insertion mutation, 936_937insG, in exon 9 of the SIL1 gene in all three.

2. Methods

2.1. Patients

We analyzed the SIL1 gene in 3 Japanese patients with clinically definite MSS. The diagnosis of MSS was made based on clinical and neuroradiological features. Analysis of the SIL1 gene was approved by the review board for medical ethics of the Faculty of Medicine of Saga University. Because all 3 patients had mental retardation, written informed consent was obtained from each patient's parent(s) and/or sibling(s).

2.2. Sequencing

DNA was prepared from whole blood using standard protocols. We obtained primer sequences for the SIL1 gene from Dr. Senderek [5]. The coding exons and flanking intronic sequences were amplified and sequenced according to methods described in the initial report of SIL1 gene mutations

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Table 1
Clinical genetic characterization of individuals with MSS and SIL1 mutations

	MSS 1	MSS 2	MSS 3
age	38	45	48
Consanguinity(degree)	−	−	+(2nd)
sex	M	M	F
Short statue	+	+	+
Cataract	+	+	+
Psychomotor delay	+	+	+
Ataxia	+	+	+
Myopathy	+	+	+
convulsion	−	+	+
Cerebellar atrophy	+	+	+
Mutation	936_937ins G exon 9	936_937ins G exon 9	936_937ins G exon 9

using genomic DNA [5]. We sequenced all 10 SIL1 exons and their surrounding intronic borders. The purified products of PCR amplification were sequenced from both directions on automated sequencers (ABI 310; Applied Biosystems, Foster City, CA) using the ABI Prism Bidgye Terminator Cycle sequencing kit, as recommended by the manufacturer.

3. Results

The age of each patient at neurological and neuroradiological examinations is shown in the Table 1. Clinically, all 3 patients presented with key features of MSS, including cerebellar ataxia, infantile-onset cataracts, mental retardation, and short stature (Table 1). MRI of the brain revealed marked atrophy of the cerebellum, especially the vermis, in all three (Fig. 1). In addition, one patient had hypergonadotrophic hypogonadism, two had generalized convulsive seizures, and all had muscular weakness due to myopathy, as demonstrated by electromyography and MRI of the muscles (Supplementary figure). Pedigrees of the three patients are shown in Fig. 2. The family name and permanent domicile differed among the three patients, and no information indicating kinship between them was obtained. A loop of consanguinity was demonstrated only in one family, but familial occurrence of MSS was found for none of them.

Sequencing of the entire SIL1-coding region showed that all the 3 MSS patients carried the same homozygous mutation, insertion of G at the position 936_937 in exon 9 (Fig. 3), which had not been reported previously.

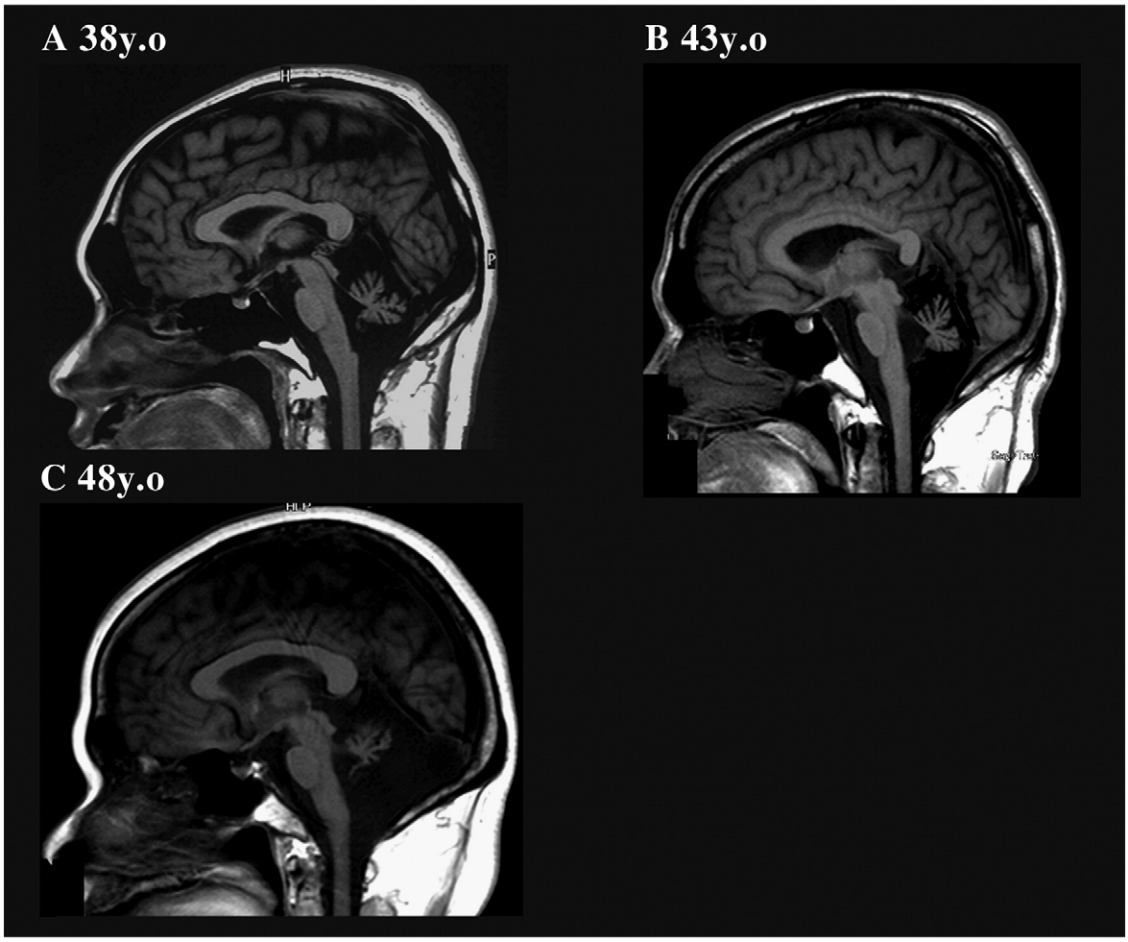

Fig. 1. Brain MRI of 3 Japanese patients with classical MSS. Marked atrophy of the cerebellum is found in all three.