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Short communication

Meiotic CAG repeat instability in spinocerebellar ataxia type 6: Maternally transmitted elongation in a presumed sporadic case

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Abstract

Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominantly inherited disorder characterized by cerebellar ataxia, dysarthria and nystagmus. The molecular background for the disorder is a CAG repeat expansion in the *CACNA1A* gene located on chromosome 19. The size of SCA6 expanded alleles is usually stable, and variation in repeat size over successive generations is rare.

We report a Danish family with one case of SCA6 resembling a sporadic case of spinocerebellar ataxia. Analysis of the *CACNA1A* gene showed meiotic CAG repeat instability in the transmission from a 70-year-old woman with no subjective symptoms to her symptomatic son. The CAG repeat size expanded from 22 repeats in the mother to 23 repeats in the proband. This case demonstrates maternal repeat instability and clinical anticipation in a family with SCA6.

Keywords: Spinocerebellar ataxia type 6; CAG repeat; Meiotic instability; SCA6

1. Introduction

Autosomal dominant cerebellar ataxia (ADCA) is a heterogeneous group of disorders characterized by autosomal dominant inheritance and progressive ataxia due to degeneration of the cerebellum and its pathways [1]. In spinocerebellar ataxia type 6 (SCA6) dysarthria and nystagmus is characteristic besides the cerebellar ataxia [2].

The molecular background of the disorder is a CAG repeat expansion in the *CACNA1A* gene located on the short arm of chromosome 19 [3]. The CAG repeat size of SCA6 disease alleles is smaller than the CAG repeat size of other SCA disease genes, and it is generally stable during intergenerational transmission [4]. The boundaries between the size of normal CAG repeat lengths and pathological expanded alleles are not clear-cut. Most authors define the normal repeat range as 4 to 18 CAG units. The clinical significance of alleles with 19 or 20 repeats is unclear (intermediate repeat range), whereas the abnormal repeat range is defined as 21 to 30 CAG units [2,5].

The *CACNA1A* gene product has a known function as part of the α_{1A} voltage-dependent calcium channel, and point mutations in the *CACNA1A* gene cause the two allelic disorders, Episodic Ataxia Type 2 and Familial Hemiplegic Migraine [6].

We report a Danish family with one case of SCA6 resembling a sporadic case of spinocerebellar ataxia and meiotic CAG repeat instability in the transmission from a 70-year-old woman with no subjective symptoms to her symptomatic son.

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2. Subjects and methods

2.1. Clinical study

The proband in the here reported Danish family with spinocerebellar ataxia type 6 was referred for neurogenetic evaluation. The clinical features of the proband and family members were obtained through interview, clinical examination, and review of medical records. All available family members were interviewed and examined by the same neurologist (JN).

2.2. Molecular genetic study

Informed consent was obtained from all individuals before genetic testing. Blood samples were collected, and genomic DNA was extracted according to standard procedures. Molecular analysis of the CAG repeat length in the *CACNA1A* gene was performed by PCR amplification using primers *S*-5-F1/*S*-5-R1 as described by Zhuchenko et al. [3]. PCR products were separated on 6% denaturing polyacrylamide gels and visualized by autoradiography using ^{33}P labelling. Allele sizes were determined by comparing migration relative to an M13 sequencing ladder.

3. Results

3.1. Clinical findings

The pedigree of the family is shown in Fig. 1. The proband (case III:1 in the pedigree) experienced progressive deterioration of gait and balance starting at age 42. The symptoms started insidiously with gait ataxia and, subsequently, he also developed dysarthria. He had no dysphagia or signs of peripheral neuropathy, and the disease had a slowly progressing course. At age 46, he was referred for neurologic evaluation because of his progressive ataxia. MRI of the brain revealed cerebellar atrophy with an intact brain stem. Laboratorial investigations for reversible and irreversible causes of ataxia including blood counts, electrolytes, liver function testing, thyroid function test, serologic markers for vitamin E and vitamin B deficiency, coeliac disease and neuroborreliosis, were all normal. The clinical examination and imaging findings were consistent with a "pure" cerebellar ataxia, and he was finally diagnosed as "ILOCA" (idiopathic late onset cerebellar ataxia).

At age 48, he was referred for neurogenetic evaluation. Neurologic examination revealed ataxic gait, severe balance difficulties, and severe dysarthria. Quantitative eye movement testing revealed hypometric saccades, but no down beat nystagmus. Prior to the diagnosis of SCA6 in III:1 the family had no knowledge of family members with similar symptoms. The father (case II:1) had Parkinson's disease and a maternal aunt (case II:3) had gait problems of unknown aetiology. She was living abroad and not accessible for examination. The patient had no knowledge about any symptoms in his maternal grandparents. He had three younger brothers and one younger sister. The three brothers were neurologically examined with a normal result. The sister is living abroad and was not accessible for examination; however, to our knowledge, she has no symptoms. The mother (case II:2) has no subjective

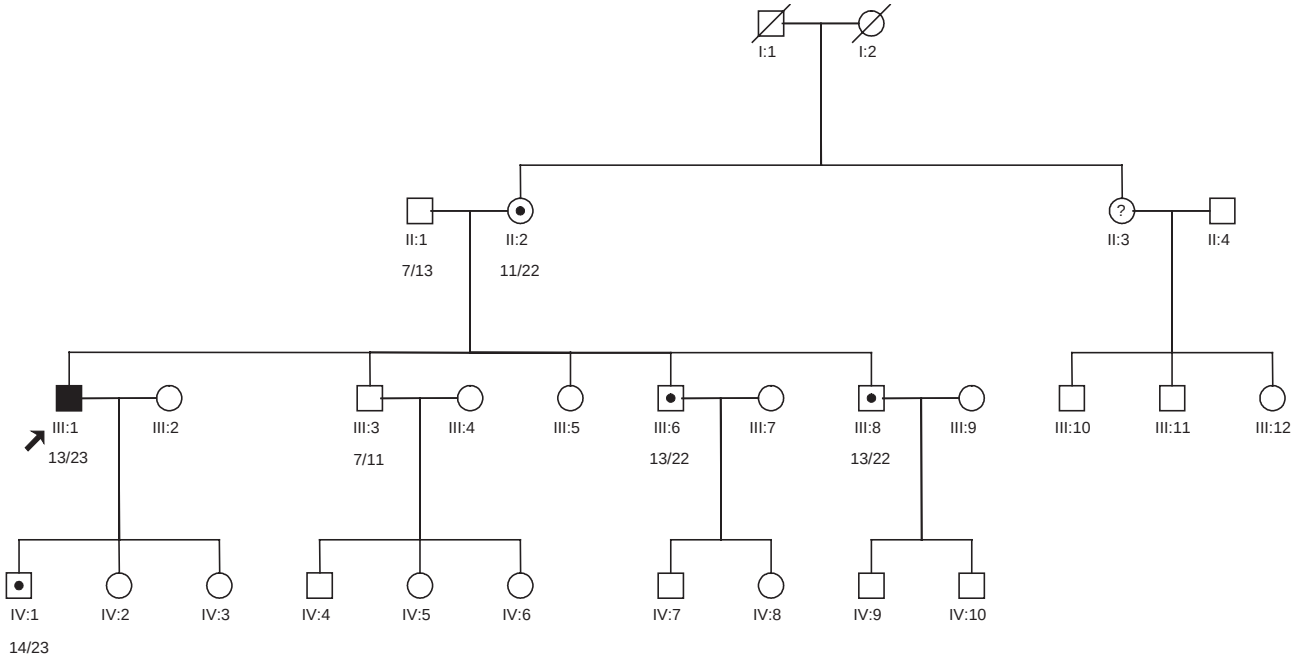

Fig. 1. Pedigree of the SCA6 family. Arrow indicates the proband; filled symbol: SCA6 patient; open symbols: asymptomatic individuals; dots: asymptomatic carriers (case II:2 has discreet abnormalities at neurological examination, but no symptoms); ? indicates possible SCA6 phenotype in an individual it has not been possible to examine. CAG repeat allele sizes are indicated with numbers (e.g. 13/23).