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A Small Trinucleotide Expansion in the TBP Gene Gives Rise to a Sporadic Case of SCA17 with Abnormal Putaminal Findings on MRI

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Abstract

A Japanese woman developed gait disturbances at 25 years of age, and subsequently underwent gradual changes in her personality. By the age of 42, she showed clear signs of dementia and cerebellar ataxia, and displayed behavioral abnormalities, choreic movements and hyperreflexia. The findings of MRI not only showed cerebellar and cerebral atrophy, but also revealed putaminal rim hyperintensity on T2-weighted images. We identified a heterozygously expanded CAG/CAA repeat (45/36) within the TATA-binding protein gene, leading to a diagnosis of SCA17. These results show that a 45 CAG/CAA repeat is pathological, giving rise to early-onset SCA17.

Key words: SCA17, CAG/CAA repeat, TATA-binding protein, putaminal rim hyperintensity

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Introduction

More than twenty genomic loci have been associated with autosomal dominant spinocerebellar ataxias (ADCA) (Search OMIM for SCA, URL http://www.ncbi.nlm.nih.gov/) and the genes involved have been identified for thirteen subtypes (1). Of these, a number result from CAG trinucleotide expansions resulting in the expression of proteins with abnormally long poly-glutamine tracts, which appear to be associated with neuronal cell death by a toxic gain-of-function mechanism. Spinocerebellar ataxia type 17 (SCA17) is caused by the expansion of a CAG/CAA repeat within the TATA-binding protein (TBP) gene (2-4). SCA17 is characterized by cerebellar ataxia, choreic movements, dystonia, parkinsonism, dementia and epilepsy (2-4). Here, we report a Japanese patient with SCA17 having a short CAG/CAA repeat expansion, and discuss the putaminal findings obtained from MRI.

Abbreviations: SCA17: spinocerebellar ataxia 17, TBP: TATA-binding protein, ADCA: autosomal dominant spinocerebellar ataxia

Case Report

A Japanese woman developed gait disturbances at the age of 25 and cerebellar atrophy was evident when a MRI scan was carried out nine years later. By the age of 42, she showed dementia, truncal and limb ataxia, choreic movements in neck, truncal body, and all of her limbs, hyperreflexia, and decreased vibratory sense. Her younger sister was healthy, and her healthy parents were not consanguineous and there is no previous history of similar neurological diseases in the family.
The patient was alert and cooperative, but cognitively impaired, obtaining a score of 16 in a Mini-Mental State Examination. Her verbal, performance, and full-scale scores of Wechsler Adult Intelligence Scale-Third Edition were 50, 47 and 44, respectively. She showed behavioral abnormalities by continuing to use stairs despite severe truncal ataxia. Examination of the optic fundi showed no abnormal findings such as sclerotic changes.

The findings of MRI showed cerebellar atrophy, diffuse cerebral atrophy, dilated third ventricle (Fig. 1) although the brainstem was relatively preserved, and no cross sign was detected in the pons. The findings also displayed symmetrical putaminal rim hyperintensity on T2-weighted and T2*-weighted images (Fig. 2). The putaminal rim lesions showed low intensity on the T1-weighted image, and on FLAIR image, the low intensity area was surrounded by isointensity (Fig. 2D). Similar putaminal rim intensities were observed in the same regions from the MRI performed previously, at the age of 34 years (Fig. 2E and F). However, the cerebellar and cerebral atrophy, and dilated third ventricle were more pronounced in the MRI carried out at the age of 42. She had no history of smoking, hypertension, hypercholesteremia, or diabetes mellitus.

Blood samples were obtained from the patient with informed consent and genomic DNA was extracted by the standard method. SCA1, SCA2, SCA3, SCA6, DRPLA and Huntington’s disease were ruled out genetically. We amplified the genomic region of the TATA-binding protein (TBP) gene containing CAG/CAA repeats by polymerase chain reaction (PCR) as described previously (5), and subcloned and sequenced the PCR products using the TA vector (Invitrogen, Carlsbad, CA). The patient was found to possess a heterozygously expanded CAG/CAA repeats (45/36) within the TBP gene, leading to a diagnosis of SCA17. The configurations of the CAG/CAA repeats were (CAG)₉(CAA)₉(CAG), CAACAGCAA(CAG)₂, CAACAG, and (CAG)₁₆(CAA), (CAG)₉(CAA)₉(CAG)₂, CAACAG, respectively. In a similar fashion the TBP gene of her mother was analyzed, revealing that she had 39/36 repeats; (CAG)₉(CAA)₉(CAG), CAACAGCAA(CAG)₂, CAACAG and (CAG)₁₆(CAA), (CAG), CAACAGCAA(CAG)₂, CAACAG. We were unable to genetically examine her father.

Discussion

The present case was genetically diagnosed with SCA17 as she possessed a small CAG/CAA repeat expansion (45 repeats) within the TBP gene. She developed the disease at a relatively young age (25 years) and displayed typical clinical features of SCA17 such as personality change, dementia, choreic movements, cerebellar signs and hyperreflexia. A previous study of eight Japanese SCA17 cases revealed that 44 repeats can be pathogenic, but also suggested that with 44-47 repeats the disease may not be fully penetrant (6). The configuration of the mother’s CAG/CAA repeats suggests that the disease allele of the patient originates from her father, however he could not be genetically examined and so we do not know whether he may have possessed the expanded repeat and was asymptomatic or he possessed an intermediate allele that became expanded through paternal transmission. These results confirm that a shorter repeat expansion can give rise to SCA17.

The findings of MRI in the present case also showed symmetrical putaminal rim hyperintensity on the T2-weighted image as well as cerebellar atrophy and diffuse cerebral atrophy. These lesions were also detected when she was 34 years of age, and displayed low intensity on the T1-weighted image. On the FLAIR image, the low intensity areas were surrounded by isointensity. These MRI findings could result from enlarged periventricular or Virchow-Robin (VR) spaces (7), which become increasingly common with age, and are often associated with hypertension, cerebral ar-
Figure 2. Symmetrical hyperintense areas were observed in the bilateral putaminal rims on the T2-weighted (white arrows in A and E) and T2*-weighted images (B). The lesions are recognized as low intensity on the T1-weighted images (C and F) and as low intensity surrounded by isointensity on the FLAIR images (D). MRI performed at 34 years of age (E and F).

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References