Short Communication

Mutation Analysis of the TATA box-binding protein (TBP) gene in Chinese Han patients with spinocerebellar ataxia

Q. Xu a,1, X.H. Li a,1, J.L. Wang a, H. Jiang a,c, S. Zhang a, L.F. Lei d, L. Shen a,c, K. Xia b, Q. Pan b, Z.G. Long b, B.S. Tang a,b,c,*

a Department of Neurology, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha 410008, Hunan, China
b National Laboratory of Medical Genetics, Central South University, Changsha, Hunan, China
c Neurodegenerative Disorder Research Center, Central South University, Changsha, Hunan, China
d Department of Neurology, Xiangya Third Hospital, Central South University, Changsha, Hunan, China

1. Introduction

Spinocerebellar ataxias (SCAs), are a highly heterogeneous group of neurodegenerative disorders that share clinical characteristics of progressive deterioration in gait and balance, and varying combinations of the involvement of the cerebrum, extrapyramidal system, bulbar system, spine, and peripheral nervous system. Several types of SCAs (SCA1, 2, 3, 6, 7, 12, 17) and dentatorubral-pallidoluysian atrophy (DRPLA) are caused by abnormal repetitions of the trinucleotide bases cytosine–adenine–guanine (CAG), which results in an expansion of the corresponding gene. Although SCA3 is the most common type of autosomal dominant SCA in mainland China, SCA17 has still not been identified. To determine the prevalence of SCA17 in patients in mainland China, we examined the CAG/CAA repeats in the TATA box-binding protein (TBP) gene of 263 patients with cerebellar ataxia. The study comprised 263 patients who had been cleared for mutations on SCA1, 2, 3, 6, 7, 12 and DRPLA and 110 healthy adults.

2. Study method and population

From January 1995 to June 2008 we recruited 501 spinocerebellar ataxia patients (306 unrelated patients with autosomal dominant cerebellar ataxia and 195 patients with sporadic ataxia) and performed SCA1, 2, 3, 6, 7, 12 and DRPLA gene analysis on them. As a result, we were able to exclude expansion of the CAG repeats of SCA1, 2, 3, 6, 7, 12 and DRPLA genes in 100 unrelated probands and 163 sporadic patients and to further analyse them for CAG/CAA repeats in the TBP gene. Analysis of CAG/CAA expansion in this gene was performed in 263 patients consisting of 100 dominantly inherited ataxias and 163 patients with sporadic ataxias. Abnormal expansion of CAG/CAA repeats in the SCA17 locus was found in a proband and her younger sister. To our knowledge, we are providing the first kindred analysis of SCA17 in mainland China.

3. Results

There was no abnormality found in healthy controls. The distribution of CAG/CAA repeats number in the TBP gene among healthy adults in our study ranged from 26 to 43 with a peak at the allele with 34 CAG/CAA units. While SCA17 was not detected in 163 sporadic patients, an expanded repeat with 55 repeat units at the TBP locus was detected in a single index case.

The clinical features of the affected individual (a 35-year-old woman) were similar to those described so far, including typical gait ataxia, dysphagia, intention tremor, cognitive deficits, and psychiatric symptoms such as depression and insomnia. The ataxic...
symptom score, using the scale for the assessment and rating of ataxia (SARA), was 17/40, while the result of the international cooperative ataxia rating scale (ICARS) was 41/100. Her mini-mental status examination (MMSE) score was 15 with 30 as the highest score possible. Her MRI showed mild cerebellar atrophy.

We investigated the CAG/CAA repeat expansion of the TBP gene in her available family members with their informed consent (Fig. 1). We identified that the younger sister (II5) of the proband was asymptomatic, carrying the pathogenic repeat with 53 triplets. Her SARA score was 4/40, her ICARS scale score was 9/100 and her MMSE score was 23/30; however, the MMSE score had little to no value because she was illiterate. Her brain MRI displayed no abnormalities.

The proband’s father (I1) first showed gait disturbances and dysarthria at the age of 50 years, with slow progression. This indicated that her father presumably had the same disease. Unfortunately, her father died from another disease at age 54 several years before the study.

4. Discussion

To date, molecular screening of SCA17 has been performed among patients of a number of ethnic origins, including European,4,5 Japanese,4,5 American6 and Brazilian.7 Taiwan also reported sporadic patients with abnormal CAG/CAA repeats in the TBP gene.8 In our analysis of patients with SCA17 in mainland China, we found an abnormal expansion number of CAG/CAA repeats in the SCA17 locus in a proband (55 repeats) and her younger sister (53 repeats).

The instability of the CAG repeat is the molecular basis of a phenomenon called “anticipation”. Compared to the other SCA subtypes caused by expanded trinucleotide repeats, anticipation in SCA17 kindreds is rare because the interruption of CAA within the CAG repeat configuration of the TBP gene is considered significant in stabilizing the microsatellite.9 The most common CAG repeat configuration in SCA17 patients is: (CAG)3(CAA)3(CAG)n1, CAACAGCAA(CAG)n2CAACAG. Alleles without the characteristic CAA-CAG-CAA interruption will change the expanded allele size during intergenerational transmission. Individuals affected by SCA17 in our reported kindred harbored a novel configuration of (CAG)3(CAA)3(CAG)6CAA(CAG)nCAACAG, which also lacked the interruption of CAA-CAG-CAA. This finding is consistent with the presence of anticipation in this kindred. The patient I1 had disease onset in his 50s, but his two affected daughters in their 30s (patients in generation II), presented faster progression, especially with respect to the proband. We presume that the proband’s father, who had mild clinical symptoms as well as late-onset disease, might have had a smaller expanded allele. Unfortunately, the CAG/CAA repeat of the proband’s father is unknown.

In conclusion, considering the result of our screening for the CAG/CAA expansion in the SCA17 gene in Chinese Han population, SCA17 appears rare in China, with a ratio of 1/501. To our knowledge we are providing the first SCA17 kindred from mainland China and the normal allele range in the Han population.

Acknowledgements

This study was supported by grants from the National 863 High-tech Project (No. 2006AA02A408), National Basic Research Program (973 program) (No. 2006cb500700), National Science and Technology Support Project of “the Eleventh Five-year Plan” (No. 2008BA05A07) and National Natural Science Foundation of China (30671151 and 30400262).

References