Dentatorubropallidoluysian Atrophy in Chinese

I-Hui Lee, MD; Bing-Wen Soong, MD, PhD; Yi-Chun Lu, BS; Yue-Cune Chang, PhD

**Background:** Dentatorubropallidoluysian atrophy (DRPLA) is a rare, autosomal dominant neurodegenerative disease characterized by a range of clinical manifestations, including cerebellar ataxia, epilepsy, myoclonus, choreoathetosis, and dementia. Outside the Japanese population, the prevalence is extremely low worldwide. The reason for different ethnic prevalences of DRPLA is unclear. A previous assumption was that large normal alleles contribute to generation of expanded alleles and the relative frequencies of DRPLA.

**Objectives:** To describe the clinical, radiological, and genetic features of the first reported Chinese family with DRPLA, to our knowledge, and to compare the size distribution of normal alleles at the DRPLA locus in healthy Chinese individuals with that of other ethnic groups.

**Patients and Methods:** Of 80 Chinese kindreds with autosomally dominant spinocerebellar ataxias, 1 pedigree with 2 affected patients was found by polymerase chain reaction to carry the characteristic DRPLA mutation. The allele frequencies of different CAG repeat lengths at the DRPLA locus in 225 healthy Chinese individuals were also analyzed and compared with Japanese, white, and African American distributions.

**Results:** The clinical presentations of the 2 Chinese patients affected with DRPLA are similar to those described in Japanese patients, except that the affected father exhibited myoclonus but not chorea. Although the normal DRPLA allele size is distributed similarly in Chinese and Japanese populations, DRPLA in Chinese individuals is rare. Thus far, to our knowledge, only 1 intermediate-sized allele containing more than 30 CAG repeats has been reported among healthy Chinese individuals, in contrast to 3 among Japanese populations.

**Conclusion:** The ethnic prevalence of DRPLA seems to be correlated with the prevalence of intermediate-sized alleles in individual populations.

Arch Neurol. 2001;58:1905-1908

**DENTATORUBROPALLIDOLUYSIAN atrophy (DRPLA) is a neurodegenerative disorder with characteristic neuropathological findings of combined degeneration of the dentatorubral and pallidoluysian systems of the central nervous system.** The clinical symptoms are diverse, with varying combinations of myoclonus, epilepsy, ataxia, choreoathetosis, and dementia. The prevalence of DRPLA has been estimated to be 2 to 4 per 1 million Japanese, a rate similar to that of Huntington disease in Japan. Outside Japan, DRPLA remains rare, with previous reports of only 8 white kindreds and 1 African American family with Haw River syndrome. The reason for different ethnic prevalences of DRPLA is unclear.

A molecular defect in patients with DRPLA, identified in 1994, lies in the expansion of an unstable (CAG), repeat in the DRPLA gene on chromosome 12p. A correlation between age at onset, severity of disease, and repeat size has been documented. Despite the demonstration of a common molecular defect in patients with DRPLA, clinical and neuropathological differences have been reported among these patients, even within a family. There are also different ranges of normal CAG repeat lengths in different ethnic groups. Herein, we describe the clinical, radiological, and genetic features in the first reported Chinese family with DRPLA, to our knowledge, and compare the distribution of CAG repeat lengths at the DRPLA locus in healthy Chinese individuals with that of other ethnic groups.

**REPORT OF CASE**

The 29-year-old patient had been well except for an episode of febrile convolution during childhood. At age 27, he began to experience episodes of loss of consciousness with generalized convulsions. Subsequently, he developed progressively unsteady gait and intellectual deterioration.
SUBJECTS AND METHODS

SUBJECTS

After informed consent was obtained, blood samples were collected from 80 kindreds with autosomal dominant spinocerebellar ataxias (SCAs) and 225 unrelated healthy Chinese individuals in Taiwan. All were descendants of Han Chinese who had emigrated from mainland China to Taiwan in the past 400 years. The diagnosis of autosomally dominant SCA was determined by history taking and clinical examination by an experienced neurologist. DNA was extracted from leukocytes by standard procedures.19

MOLECULAR STUDIES

Polymerase chain reaction was performed to identify the DRPLA alleles using CTG-B37 primers.9 To accurately assess the size of the alleles, we sequenced at least 2 independent clones for each allele in the patients. The genomic DNA was amplified using each of the primer sets and then subcloned and sequenced. Sequencing reactions were performed using a DNA sequencing kit (Sequenase version 2.0; United States Biochemical, Cleveland, Ohio).

STATISTICAL ANALYSIS

We used the log-linear model (with ln(n) as the offset)13 to explore the differences in the distribution of normal CAG repeat lengths at the DRPLA locus among Chinese, African American, white, and Japanese ethnic groups.15

RESULTS

The number of CAG repeats in the DRPLA genes from 225 unrelated healthy Chinese individuals (450 chromosomes) ranged from 6 to 23, with a bimodal distribution and peaks at 10 and 15 (Figure 2). The heterozygosity was 90%. The frequency of alleles with more than 19 CAG repeats was 4%. No intermediate-sized alleles with more than 30 repeats were found in this series.

The stability of CAG repeats of the DRPLA genes between generations was studied in 17 healthy Chinese families. There was no expansion or contraction of the repeats in 31 normal-appearing meioses.

Among the 80 Chinese kindreds with autosomally dominant SCAs, 1 kindred (1%) containing 2 patients with DRPLA in 2 generations was found. A genetic study of the 2 patients (father and son) showed normal and expanded CAG repeats, 17 and 63 in the son and 20 and 58 in the father (Figure 3).

Based on the log-linear model analyses, among healthy persons, no significant difference in the CAG repeat length distribution at the DRPLA locus was found between Chinese (450 chromosomes) and Japanese (407 chromosomes) individuals (P>.05). However, significant differences were found between Chinese and African Americans (103 chromosomes, P<.001) and between Chinese and whites (100 chromosomes, P=.001).

COMMENT

The number of CAG repeats at the DRPLA locus on normal chromosomes varies widely among different ethnic groups. In healthy populations, the number of repeats ranges from 6 to 26, while in affected individuals it ranges from 45 to 88.3,10,11,13 The reported age of onset ranges from 1 to 62 years.10,11 In this Chinese family, marked clinical anticipation (34 years) was observed, with an increase in CAG repeats of 5 units. Similar observations have been made previously, with a mean±SE difference in age at onset of the disease between children and their fathers of 33.3±1.9 years.17 and an increase in the repeat length of more than 5 units in 80% of cases of paternal transmission.10 Thus far, all of the trinucleotide repeat disorders, except Kennedy disease and SCA type 6, have been shown to demonstrate meiotic instability. Greater instability of the CAG repeat has been found during spermatogenesis, which correlates well with a stronger clinical anticipation in paternally transmitted cases, as seen in Huntington disease, SCA1, and DRPLA.8,9,18 However, the single repeat increase in the expanded DRPLA gene seems to be more effective in producing neuronal cell damage than the changes in the Huntington disease and SCA1 genes.10

Although molecularly ascertained, our patients had several minor but distinctive clinical and radiological dif-

As the patient’s symptoms progressed, he became bedridden at age 34 and was almost mute and apathetic by age 37. The father died of pneumonia at age 71, and no autopsy was performed.

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One year later, his father, at age 61, started to manifest progressive ataxia and mental deterioration. Myoclonus and seizures developed in the subsequent 1 to 2 years. Reportedly, the father’s parents had survived into their 80s without major illness. No other family members were known to be affected.

Three years after the onset, neurologic examination of the son revealed mild to moderate memory and cognitive impairment, slurred speech, truncal and limb ataxia, and generalized hyperreflexia without focal weakness. Intermittent myoclonic jerks in the extremities were also noted. Physical examination revealed no ophthalmoplegia, nystagmus, cogwheel rigidity, or Babinski sign. No cherry-red spot or macular degeneration was found on fundal examination. A sleep electroencephalogram with polysomnography showed intermittent rhythmic delta activities and focal sharp waves in bilateral frontal regions. Magnetic resonance imaging studies revealed mild generalized brain tissue loss, especially in the cerebellum and brainstem (Figure 1). Electromyographic findings, somatosensory evoked potentials, and nerve and muscle biopsy results were all normal.

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ferences from other reported kindreds with DRPLA. The affected son presented with a progressive myoclonic epilepsy syndrome characterized by a combination of epilepsy, myoclonus, and mental deterioration, whereas the father exhibited cerebellar ataxia and dementia at the onset of symptoms and mild myoclonus and seizures later in the course of disease. It is unusual to observe seizures in patients with onset of DRPLA in the seventh decade of life. Neither patient manifested chorea, and the predominant movement disorder was myoclonus. In contrast, chorea was present in most kindreds, and myoclonus was rare in non-Japanese patients with DRPLA.1,3-6 Moreover, 11 years after the onset of symptoms, there was still no abnormal signal intensity in subcortical white matter on T2-weighted magnetic resonance imaging of the affected son. This differs from previous reports4,19 in which white matter changes were often detected in patients with onset of DRPLA in adulthood. Others have observed that the white matter changes are observed frequently in patients with late-adult onset of DRPLA many years after the onset and that such white matter changes are rarely detected in young-adult onset.20 Patient age and the size of the expanded repeat in the DRPLA gene affect the occurrence of the white matter changes.20

In this study, 4% of the Chinese DRPLA alleles had more than 19 repeats. Other studies2,13 (654 chromosomes) from different areas of China have found similar results. According to one study,16 more than 19 repeats were found in 7.4% of Japanese alleles (407 chromosomes), in 1% of African American (103 chromosomes), and in no alleles in whites (100 chromosomes). Using the log-linear model, we found no significant dif-
ference in the distribution of CAG repeat lengths at the DRPLA locus on normal chromosomes between healthy Chinese and Japanese individuals (P > .05), but found significant differences between Chinese and African Americans (P < .001) and between Chinese and whites (P = .001). The prevalence of DRPLA is higher in Japan than elsewhere in the world. Burke et al.10 have proposed that the larger alleles in the Japanese population are the source of the expansion into the pathologic DRPLA range, which might explain the difference in disease prevalence. Theoretically, the prevalence of DRPLA in Chinese kindreds should be equivalent to that in Japanese.11 However, no cases of DRPLA have been previously reported in Chinese kindreds, to our knowledge.2,23 In healthy Japanese, intermediate-sized alleles with 32, 34, and 35 CAG repeats have been reported.9,16 Although no similar intermediate-sized alleles were found in our series, a previous report2 of another healthy Chinese population of Han origin from mainland China found one such allele with 33 repeats in a DRPLA gene. Therefore, the prevalence of intermediate-sized alleles at the DRPLA locus seems to correlate with the prevalence of the disease in individual ethnic groups. This would fit with previous ideas about the mechanism of triplet repeat expansion that new mutations arise from long “normal” or intermediate alleles.22 More convincing evidence would be the existence of linkage disequilibrium or haplotype sharing between this affected family and those intermediate alleles. However, those intermediate alleles were not available to us during this study. Therefore, it is possible that the ancestral intermediate allele of this family is different from the other intermediate alleles described herein. Preliminary haplotype analyses (data not shown) have revealed that, similar to the Japanese and white kindreds with DRPLA, the expanded repeat from this Chinese family and the large normal repeats in the general Chinese population were associated with the same haplotype (A1/B1).23 The fact that DRPLA mutations in Japanese, Chinese, and whites arise more frequently on chromosomes with specific DNA haplotypes would support the hypothesis that DRPLA alleles, similar to other trinucleotide repeat disorders, may have originated from a common ancestral chromosome.24,25

Accepted for publication May 2, 2001.

This research was supported by grants NSC 89-2314-B010-027 from the National Science Council, Taipei, Taiwan, Republic of China, and VGH88-415-15 and VGH89-389-10 from Taipei Veterans General Hospital, Taiwan, Republic of China.

We thank the family, whose collaboration was essential to our study. We also thank Ruth Soong for her technical assistance.

Corresponding author and reprints: Bing-Wen Soong, MD, PhD, The Neurological Institute, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Rd, Taipei, Taiwan 112, Republic of China (e-mail: bwsoong@vghtpe.gov.tw).

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