Genetic Analysis of a Dentatorubral-Pallidoluysian Atrophy Family: Relevance to Apparent Sporadic Cases

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Dentatorubral-pallidoluysian atrophy (DRPLA) is associated with an unstable CAG trinucleotide sequence. We describe a DRPLA family whose members have an allele containing an expanded CAG repeat, even in an elderly neurologically normal individual. The proband developed DRPLA at age 14. She was initially considered a sporadic case, but later her sister became symptomatic. Investigation of the number of CAG repeat units in her family revealed the 81-year-old father to have an expanded CAG repeat of 51 units. To our knowledge, such an advanced aged unaffected patient has not been previously documented. The present example may explain apparent sporadic cases.

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Introduction

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder. The chief pathologic findings are atrophy of the dentato-rubral and pallidoluysian systems (1), and clinical characteristics may include a variety of symptoms including progressive dementia, epilepsy, cerebellar ataxia, and involuntary movements (chorea, athetosis, and myoclonus). Initial symptoms and clinical manifestations vary within individual families. Decreasing age of onset and increasing disease severity in successive generations ("anticipation") is a characteristic feature. Although the underlying mechanisms have been unclear, expansion of repeat units of a CAG trinucleotide sequence on chromosome 12p has recently been associated with the disease (2, 3). The age of onset and clinical course are correlated closely with repeat size (4), and anticipation is associated with intergenerational instability of CAG repeats. According to previous reports, the normal range of CAG repeat units is from 7 to 35, while in DRPLA patients CAG repeat numbers range from 49 to 79 (2-4). Thus, no overlaps are known in numbers of CAG repeat units between normal chromosomes and DRPLA chromosomes (4).

In this study we analyzed CAG repeat units of nine individuals of a Japanese DRPLA family in two generations. The proband, a 33-year-old woman, developed epilepsy at age 14. Her 39-year-old sister presented with ataxia and athetosis at age 38. Although both parents of the patients are neurologically normal, the 81-year-old father was demonstrated to have 51 CAG repeat units. Identification of an unaffected patient as the parent of a DRPLA patient with DNA analysis is a rarely reported occurrence.

Case Report and Methods

The pedigree is shown in Fig. 1. I-1 is a 81-year-old male who is neurologically normal. A computed tomography (CT) scan image at age 80 showed mild diffuse brain atrophy, typical for his age, without any white matter lesions. Both parents and a brother of I-1 are deceased, and there was no information indicating that they had suffered any neurological disorders. I-2 is a normal woman. II-6 is a 39-year-old woman who presented with symptoms at age 38. Chief findings on examination were truncal ataxia, muscular hypotonia, slurred and scanning speech, and choreoathetosis upon walking. II-8, the proband is a 33-year-old woman who developed progressive dementia and generalized seizures at age 14. From age 22, she experienced myoclonic involuntary movements and severe
ataxia, while from age 26, she has occasionally displayed confusion and stupor. In an apallic state at present, she frequently shows choreoathetosis and myoclonus. II-1, 2, 3, 4, 5, and 7 have no neurological deficits. Informed consent was obtained from all subjects (three males and six females). Their ages at the time of the study ranged from 33 to 81 years.

DNA was extracted from leukocytes. Polymerase chain reaction (PCR) amplification using primers for B37 (5) and analysis of the CAG repeat were performed for nine individuals in two generations. The method of assay was based on the article by Koide et al (2). II-4 was not studied.

Results

Polyacrylamide gel electrophoresis results are shown in Fig. 2. The CAG repeat size for I-1 was 15/51; I-2, 10/15; II-1, 10/53; II-2, 10/15; II-3, 15/53; II-5, 10/15; II-6, 15/60; II-7, 15/15; and II-8, 10/67. Only subjects I-1, II-1, II-3, II-6, and II-8 had an expanded allele.

Discussion

Patient II-8 who showed clinical features of progressive myoclonic epilepsy (PME) (6) had a repeat size of 67. Patient II-6, with 60 repeat units, had a relatively late age of onset with mostly ataxia and choreoathetosis. Both II-1 and II-3 were found to have 53 repeat units and showed no clinical symptoms, though they may become affected in the future and require careful observation.

Because no neurologic abnormality was evident in either parent, patient II-8 initially seemed to be a sporadic case. Later gene analysis revealed that her 81-year-old father had CAG repeats expanded to 51. This expansion is relatively short compared with the previously reported DRPLA patients; this could be the reason why he has not been affected. When the expansion was transmitted to his daughters, repeat numbers exceeded the DRPLA threshold. This example may explain the origin of sporadic cases. Although many sporadic DRPLA patients have been described, DNA analysis of both parents has rarely been performed. The only case reported by Ikeuchi et al (4) and

Figure 1. Pedigree of the dentatorubral-pallidoluysian atrophy family. Filled symbols indicate affected individuals; unfilled, unaffected; circles, females; squares, males. Ages at the time of the study are shown beneath the symbols.

Figure 2. Analysis of polymerase chain reaction products containing the CAG repeats of dentatorubral-pallidoluysian atrophy family members. At the top, the pedigree is shown in condensed form. Four lanes on the left side are M13 sequence ladders. Control 1 contains 12/17 CAG repeats; 2, 15/54; and 3, 13/76. Repeat numbers are indicated. CAG repeat size of I-1 is 15/51; I-2, 10/15; II-1, 10/53; II-2, 10/15; II-3, 15/53; II-5, 10/15; II-6, 15/60; II-7, 15/15; and II-8, 10/67.
Shimizu et al (7) described a 66-year-old unaffected father who had 59 repeat units. Shimizu et al proposed three possible expansion mechanisms: firstly, expansion via intermediate alleles, secondly, via asymptomatic fully expanded alleles, and thirdly, de novo mutation from normal alleles (7). The present case supports their second hypothesis. Intermediate alleles which contain CAG repeat expansions larger than the normal range but smaller than the disease range have been identified in Huntington's disease (8, 9), but such an occurrence in DRPLA has not been reported.

To date, no overlaps between ranges of repeat units in DRPLA chromosomes and normal chromosomes have been acknowledged. As our subject I-1 is asymptomatic at age 81 years, the “non-overlap theory” may be disproved. Burke et al have suggested that the high prevalence of DRPLA in Japanese reflects larger numbers of CAG repeat units in the normal Japanese population (10). Therefore, identification of an unaffected patient of advanced age is noteworthy, and the present family can be taken as a pointer to the origin of sporadic DRPLA cases.

References