# Dentatorubral-Pallidoluysian Atrophy: Clinical Features Are Closely Related to Unstable Expansions of Trinucleotide (CAG) Repeat

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**Dentatorubral-pallidoluysian atrophy is an autosomal dominant neurodegenerative disease characterized by various combinations of ataxia, choreoathetosis, myoclonus, epilepsy, and dementia as well as a wide range of ages at onset. A specific unstable trinucleotide repeat expansion in a gene on the short arm of chromosome 12 was recently identified as the pathogenic mutation for this disease. We investigated how the degree of expansion of the CAG repeat affects the clinical manifestations of dentatorubral-pallidoluysian atrophy. The size of the expanded alleles was well correlated with the age at onset ($r = -0.696, p < 0.001$). Patients with the progressive myoclonus epilepsy phenotype had larger expansions (62–79 repeats) and an earlier age at onset (onset before age 21). Furthermore, most of the patients with the progressive myoclonus epilepsy phenotype inherited their expanded alleles from their affected fathers. On the other hand, patients with the non–progressive myoclonus epilepsy phenotype showed smaller expansions (54–67 repeats) and a later age at onset (onset at or after age 21). Detailed analyses of clinical features demonstrated that ataxia, involuntary movement of either myoclonus or choreoathetosis, and intellectual decline are cardinal features of dentatorubral-pallidoluysian atrophy, with myoclonus and epilepsy being observed more frequently in patients with an earlier age at onset. Thus the wide variation in clinical manifestations of dentatorubral-pallidoluysian atrophy can now be clearly explained based on the degree of CAG repeat expansion, which strongly indicates that the expanded alleles are intimately involved in the neuronal degeneration in dentatofugal and pallidofugal systems.**

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Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare devastating autosomal dominant neurodegenerative disorder characterized by variable combinations of myoclonus, epilepsy, cerebellar ataxia, choreoathetosis, dementia, and psychiatric symptoms. DRPLA was first described by Smith and coauthors [1, 2] on the basis of neuropathological findings characterized by neuronal degeneration in dentatorubral as well as pallidoluysian systems. Although the first case of DRPLA described by Smith and coauthors [1] was a sporadic one, the hereditary form of DRPLA was described by Naito and Oyanagi in 1982 [3]. Since then, hereditary DRPLA has been documented predominantly among Japanese individuals [4–8] and the prevalence rate has

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been estimated to be approximately 0.2 to 0.7/100,000 in Japan [9], which is comparable to that of Huntington's disease (HD) in Japan [10].

The most characteristic clinical feature of DRPLA is the considerable heterogeneity in the clinical manifestations as well as the ages at onset. It should be noted that these variable phenotypes of DRPLA can appear even within the same family [3, 7].

Recently we and others discovered that DRPLA is caused by an unstable CAG repeat expansion in a gene on the short arm of chromosome 12 [11, 12]. To better understand the heterogeneity of clinical manifestations of DRPLA based on the degree of CAG repeat expansion, we studied 65 patients with DRPLA, including 6 with apparently sporadic disease and 1 homozygous for DRPLA.

## Patients and Methods

### *Patients*

We analyzed 59 patients with a family history of DRPLA from 28 Japanese families (Families Fj [7]; Iz, Km, Ks, and Mr [8]; Mt, Mz, Nm, and Ok [13]; Sk [14]; Sm, St, Nk, As, Ys, Um, Ay, Ts, Kd, Kr, Uj, Fj, Ot, In, Sr, Ow, Th, and Wa [15, 16]) and 6 Japanese patients with sporadic DRPLA (Patients Kb [17]; Og, Tk, Ty, and Eb [18]; and Ar) without a family history of neurological diseases. Diagnosis of DRPLA was initially made prior to molecular diagnosis in 57 patients based on either the clinical findings or the pathological diagnosis of autopsied brains. Molecular analysis confirmed the diagnosis of DRPLA in these 57 patients. In the remaining 8 patients including the 6 with sporadic disease, the diagnosis was initially made on the basis of molecular analysis of the CAG repeat in the DRPLA gene. Two patients with hereditary DRPLA were initially diagnosed as having schizophrenia because they showed only a mild neurological sign of tremor and their psychiatric symptoms were typical of schizophrenia.

Informed consent was obtained from all of the subjects. The patients' ages at the time of the study ranged from 11 to 79 years. Thirty-six of the patients were female and 29 were male. Age at onset was defined as the age when the first clinical symptoms were noticed. Clinical manifestations including myoclonus, epilepsy, choreoathetosis, ataxia, mental retardation or dementia, and psychiatric symptoms were carefully evaluated either by direct investigations by us or by analyses of hospital records.

The progressive myoclonus epilepsy (PME) phenotype is defined as a phenotype in which myoclonus, epilepsy, and intellectual decline are the initial clinical features and precede the appearance of ataxia or choreoathetosis. The non-PME phenotype is defined as a phenotype with ataxia and choreoathetosis being the initial and major clinical manifestations.

### *Molecular Analysis*

Genomic DNA was isolated from either leukocytes or frozen autopsied cerebral cortex tissues. Polymerase chain reaction (PCR) amplification and analyses of the CAG repeat in the DRPLA gene were performed as described previously [11, 19].

Previous observations by us [11] and others [12] indicated that normal alleles of the CAG repeats range in size from 7 to 34 repeats and that the expanded alleles in the DRPLA patients range in size from 49 to 75 repeats. In the present study, molecular diagnosis of DRPLA was made for those having alleles larger than 49 repeats.

### *Statistical Analysis*

Statistical analyses including calculation of Pearson's correlation coefficient, linear regression analysis, and Mann-Whitney analysis were performed using SPSS version 6.01.

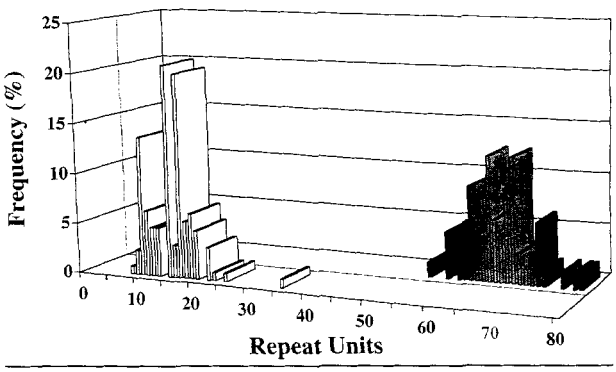
## Results

### *Expansion of CAG Repeat Is Well Correlated with Onset Age*

As shown in Figure 1, 62 normal individuals showed CAG repeats in the DRPLA gene ranging in size from 8 to 35 repeats, with a bimodal distribution exhibiting peaks at 10 and 15 repeats. All 65 DRPLA patients showed CAG repeat expansions ranging in size from 54 to 79 repeats. On the other hand, the normal alleles of the patients ranged in size from 6 to 24 repeats. There was a considerable variation in age at onset (median = 30 years, range = 1–62 years, n = 63), and we observed a strong inverse correlation between the number of CAG repeats and age at onset ($r = -0.696$, $p < 0.001$, n = 62). There was no correlation of the age at onset with the size of unexpanded alleles.

Twenty-nine (76.6%) of the 39 patients with expanded alleles larger than 61 repeats showed the PME phenotype except for 1 patient who was homozygous for a 57-repeat allele. Twenty-two (75.9%) of the 29 DRPLA patients showing the PME phenotype inher-

*Fig 1. Distributions of number of CAG repeats. Frequency distributions are shown for the number of CAG repeat units observed for 66 DRPLA chromosomes and 124 normal chromosomes.* Shaded bars *represent DRPLA chromosomes;* open bars, *control chromosomes.*



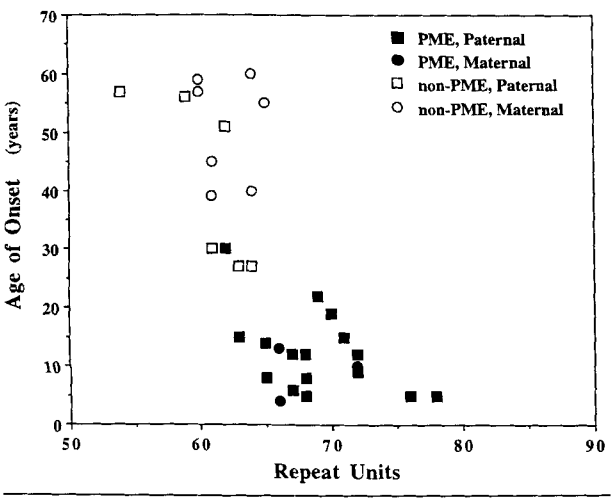
ited their disease genes from their affected fathers (Fig 2).

*Genetic Anticipation Is Based on the CAG Repeat Expansion and Larger Expansion Frequently Occurs with Paternal Transmission*

Based on the analysis of ages at onset in the DRPLA patients in our cohort, an average of −22.9 years of acceleration per generation was demonstrated. The acceleration of age at onset was more prominent for paternal transmission (median = −28.0 years, range = −47–+17, n = 27) compared to maternal transmission (median = −17.0 years, range = −27–+14 years, n = 9). In a review of the literature, quite similar results were observed (median = −29.0, range = −44–+0, n = 27 for paternal transmission; median = −13.0, range = −23–−12, n = 11 for maternal transmission) [20–28]. Statistically significant differences were found between paternal and maternal transmissions both in our cohort ($p < 0.05$) and in the literature ($p < 0.01$).

In the present study, we were able to compare numbers of CAG repeat units and ages at onset of parents and their offspring in 16 meiotic events for paternal transmission and in 4 meiotic events for maternal transmission. When the differences in the sizes of CAG repeats were compared between paternal transmission (median = +5.0, range = +1–+14, n = 16) and maternal transmission (median = +2.0, range = −3–+4, n = 4), a statistically significant difference ($p < 0.05$) was found (Fig 3).

*Fig 2. Correlation of numbers of CAG repeat units with age at onset, parental origins, and clinical phenotypes. Parental origins were unambiguously determined for 50 patients with dentatorubral-pallidoluysian atrophy. Age at onset, parental origins, and clinical phenotypes (progressive myoclonus epilepsy [PME] or non-PME) were analyzed in comparison with numbers of CAG repeat units.*



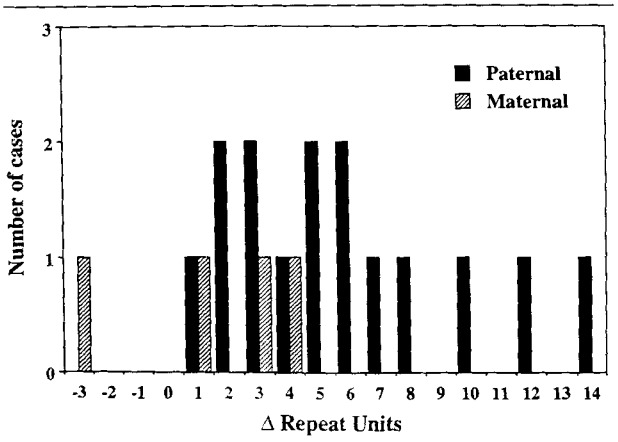




*Fig 3. Parental bias of intergenerational change of the number of CAG repeat units during paternal and maternal transmissions.*

*Degree of CAG Repeat Expansion Is Well Correlated with Clinical Features*

As shown in Figure 2, patients with an earlier age at onset (onset before age 21) frequently showed the PME phenotype, whereas patients with a later age at onset (onset at or after age 21) frequently showed the non-PME phenotype. To characterize the heterogeneity in its clinical manifestations more precisely, we divided the 62 DRPLA patients into three groups depending on age at onset (Group 1: onset before age 21; Group 2: onset at 21–40 years; and Group 3: onset after 40). We determined whether the patient showed myoclonus, ataxia, choreoathetosis, epilepsy, psychiatric symptoms, or dementia at the time of the most recent neurological examination. Mean intervals from the age at onset when the first clinical symptom was noticed to most recent examination of presence of symptoms were 15.5 years for Group 1, 11.6 years for Group 2, and 9.4 years for Group 3.

Figure 4 shows the frequencies of these symptoms in each group classified according to age at onset. Patients in Group 1 (onset before age 21) exhibited myoclonus (96%) and epilepsy (96%) much more frequently than did patients with a later age at onset (Groups 2 and 3). On the other hand, patients with an age at onset after 40 exhibited choreoathetosis (80%) and psychiatric symptoms (80%) much more frequently than did patients with an earlier age at onset (Groups 1 and 2). It is noteworthy that ataxia and dementia were frequently observed in all three groups irrespective of age at onset. Furthermore, when myoclonus and choreoathetosis were combined as involuntary movements, most patients (90.8%) were found to show involuntary movements of either type irrespective of age at onset.

Thirty-nine (73.6%) of 53 patients in whom we were able to analyze psychiatric symptoms in detail showed

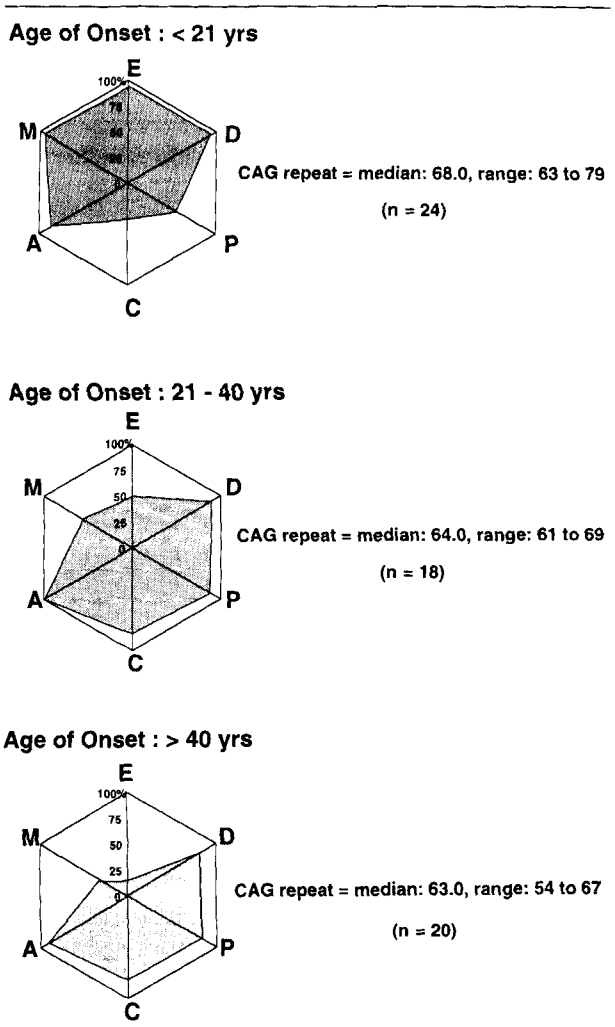



*Fig 4. Frequencies of the cardinal clinical features of dentatorubral-pallidoluysian atrophy (DRPLA) depending on age at onset. Frequencies of the six cardinal clinical symptoms of DRPLA, which include myoclonus* (M), *epilepsy* (E), *ataxia* (A), *choreoathetosis* (C), *dementia* (D), *and psychiatric symptoms* (P), *are shown in three groups with different ages at onset (Group 1: < 21 years; Group 2: 21–40 years; and Group 3: > 40 years).*

some psychiatric symptoms, which commonly included character changes such as instability in mood, irritability, and euphoria, and less frequently, delusion and visual or auditory hallucinations.

*Sporadic DRPLA Is Caused by Expansion of CAG Repeat in DRPLA Gene*

In the present cohort, we were able to analyze 6 patients with apparently sporadic DRPLA. Clinical features of these 6 are summarized in the Table. The patients had expanded alleles of 67, 62, 63, 64, 64, and 68 repeats. We were able to analyze only the parents of Patient Og for the CAG repeat expansion. Although her father did not show any neurological symptoms at the age of 65, he had an expanded allele of 59 repeats. Her mother had normal alleles.

*A Homozygous DRPLA Patient Shows Earlier Age at Onset and More Severe Phenotype*

In our cohort, we identified a patient who was homozygous for the expansion of the CAG repeat. The patient was born to consanguineous parents and had expanded alleles of 57 repeats as a homozygous state. Neither of his parents showed any neurological symptoms at ages 74 and 72; however, 4 of his 6 siblings had seizures followed by progressive neurological deterioration, and died before the age of 12. The age at onset for the patient was 18, and he showed a PME phenotype. Based on linear regression analysis, the age at onset is earlier than the 99% lower confidence level.

## Discussion

We showed a highly significant correlation between the size of CAG repeats in the DRPLA gene and age at onset. This is similar to the previously described correlations between age at onset and repeat sizes in HD [29–36] and spinocerebellar ataxia type 1 (SCA1) [37]. The correlation of size of the CAG repeat not only with the age at onset of DRPLA but also with the clinical manifestations (see Fig 4) indicates that CAG

*Summary of Clinical Features of 6 Patients with Sporadic Disease and 1 Homozygous Patient*

| Patient | Age (yr) | Sex | Ages (yr) of Parents | | Age (yr) at Onset | Clinical Features | | | | | | CAG Repeats | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Father | Mother | | M | E | D | A | C | P | | |
| Sporadic disease | | | | | | | | | | | | | |
| Og | 35 | F | 65 | 63 | 27 | + | − | + | + | + | − | 64 | 15 |
| Tk | 48 | F | 80[a] | 85[a] | 44 | − | − | + | + | + | + | 64 | 19 |
| Kb | 55 | F | 72[a] | 52[a] | 47 | + | + | + | + | + | + | 63 | 9 |
| Ty | 22 | F | 46 | 54 | 15 | + | + | + | + | − | − | 68 | 19 |
| Ar | 57 | F | Ages at death unknown | | 47 | + | + | + | + | + | + | 67 | 18 |
| Eb | 46 | F | 82 | 78 | 36 | + | − | + | + | + | + | 62 | 15 |
| Homozygous | | | | | | | | | | | | | |
| 7 | 38 | M | 74 | 72 | 18 | + | + | + | + | + | + | 57 | 57 |

[a]Age when he/she died.

M = myoclonus; E = epilepsy; D = dementia; A = ataxia; C = choreoathetosis; P = psychiatric symptoms.

repeat expansions are intimately involved in the pathogenesis of DRPLA.

As shown in the Results, a much larger intergenerational increase was observed with paternal transmission compared to maternal transmission, which correlates well with the genetic anticipation of DRPLA. This phenomenon was also described for HD (median = +2.0, range = 0–+16, n = 42 for paternal transmission; median = +2.0, range = 0–+8, n = 29 for maternal transmission) [29–36] and SCA1 (median = +2.0, range = −4–+28, n = 28 for paternal transmission; median = 0.0, range = −6–+4, n = 16 for maternal transmission) [37, 38]. Among the three diseases, DRPLA is the one with the largest intergenerational increase and with the most prominent anticipation. In HD, DNA from the sperm of patients was found to show considerable variations in the sizes of CAG repeats compared to DNA from somatic cells [30]. The results strongly indicate that a similar mechanism must underlie the larger intergenerational increase of the CAG repeats in male gametogenesis in DRPLA.

Since the penetrance of DRPLA has been estimated to be high (90%) [10], it has been claimed that it is difficult to make a clinical diagnosis of DRPLA in the absence of familial occurrence. On analysis of the CAG repeats, however, we identified 6 patients with sporadic DRPLA. For 1 patient (Patient Og), we were able to identify a mild expansion of the CAG repeat in her father's DRPLA gene, despite the fact that he did not exhibit any neurological abnormalities. The result indicates that Patient Og is the first in this pedigree to cross the phenotypic threshold due to the intergenerational increase of the CAG repeat. The presence of sporadic disease with expanded alleles indicates that we should consider the possibility of DRPLA for patients even without familial occurrence who show variable combinations of the above-mentioned clinical features.

We described a homozygous DRPLA patient. In comparison to other affected individuals with DRPLA, the age at onset for this homozygous patient was much earlier than predicted for his repeat size and the clinical manifestations were much more severe than those in patients carrying alleles of similar sizes as a heterozygous state. This is in contrast with HD for which homozygous patients show clinical manifestations no more severe than those of heterozygous patients, indicating the true dominancy of the mutation in HD [29, 39, 40]. The result raises the possibility that the gene dosage effect might be different between DRPLA and HD. Because of the consanguinity of the parents, however, there is also a possibility that genetic abnormalities other than DRPLA contribute to the phenotype of the homozygous patient.

There have been reports of several patients with hereditary DRPLA who were initially diagnosed as having HD [24, 25, 27, 41–44]. A detailed review of the literature showed that all patients diagnosed as having the "pseudo-Huntington form" in fact exhibited some preceding ataxia; careful evaluation of preceding ataxia, atrophies of the cerebellum and brainstem, in particular, pontine tegmentum, and absence of atrophy of the head of caudate nucleus may help in the differential diagnosis. However, the distinction can only be made with certainty by analyzing the CAG repeats in the DRPLA and HD genes of patients showing involuntary movements and dementia.

It is noteworthy that the DRPLA patients in our cohort frequently (73.6%) showed psychiatric symptoms. In fact, in the literature many psychiatric symptoms were associated with DRPLA. Ill-humored mood was observed in patients with the PME phenotype [22]. Euphoria [22, 24, 41, 45], soliloquy [24, 45], hypererotism [17], hyperorexia [17, 41], and suicidal tendencies [21] were noted in patients with the non-PME phenotype, whereas character change [17, 21–24, 41, 46], abnormal behavior [21, 24], delirium [24, 42, 45], delusion [16, 21, 23, 43], and visual and auditory hallucinations [3, 16, 17, 43, 46, 47] were found to be associated with both phenotypes. Since 2 patients in our cohort were initially diagnosed as having schizophrenia, molecular diagnosis of DRPLA should be applied for those presenting with various psychiatric symptoms in addition to minor neurological abnormalities.

DRPLA has predominantly been reported in Japanese individuals, but familial diseases with quite similar clinical features have been documented in other ethnic groups [48–50]. Warner and colleagues [51] recently identified 2 European families with expansions of the CAG repeat in the DRPLA gene. Expansion of the CAG repeat in the DRPLA gene in the kindred with Haw River syndrome, which shows very similar clinical and pathological features to those of DRPLA, also was confirmed by molecular analysis [48, 52]. Thus molecular analysis of the DRPLA gene may lead to identification of many more non-Japanese patients with CAG repeat expansions in the DRPLA gene.

In this study, we showed that there are good correlations of the clinical features as well as the age at onset of DRPLA with the degree of CAG repeat expansion. These results raise many intriguing questions as to the mechanisms of selective neuronal degeneration of dentofugal and pallidofugal systems and meiotic instability of the CAG repeats, which should be clarified by further investigations including creation of animal models.

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