Short report

The relationship between (CAG)_n repeat number and age of onset in a family with dentatorubral-pallidoluysian atrophy (DRPLA): diagnostic implications of confirmatory and predictive testing

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Abstract

Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare neurodegenerative disorder characterised by variability in both age of onset and clinical features. Despite the recent identification of the CAG expansion mutation in DRPLA, the number of molecularly confirmed cases remains small. Given its rarity and prominent phenotypic heterogeneity, some care needs to be exercised in the interpretation and dissemination of test results derived from direct gene testing for the DRPLA specific expansion mutation.

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Key words: DRPLA; trinucleotide repeat; phenotypic heterogeneity; DNA diagnostic testing.

Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder with a clinically heterogeneous phenotype. Core clinical features include myoclonus, epilepsy, ataxia, choreiform movements, and dementia/mental retardation. Associated findings can include psychiatric disease and subcortical white matter changes. Although originally described in kindreds of Japanese descent,^{1,2} the recent identification and subsequent molecular confirmation of DRPLA in families outside Japan underscores the probability of a wider geographical and ethnic distribution.³⁻⁶ The molecular defect in DRPLA involves the expansion of an unstable (CAG)_n repeat within a recently characterised gene on the short arm of chromosome 12.⁷ In general, there is a statistically significant correlation between (CAG)_n repeat length, clinical phenotype, and ages of onset with the largest repeats associated with the juvenile onset form of the disease.^{8,9} However, for any given repeat length, age of onset can be variable. While repeat length alone accounts for approximately 50 to 68% of the variability,^{8,9} the other factors involved in this variability are currently unknown. Possible mechanisms in-

clude the influences of mitotic instability of disease alleles in various tissues, sequence variations in the 5' and 3' regions of the DRPLA gene, *trans* acting effects of the normal gene product, or other genetic/environmental factors. As this expansion mutation has been found in all DRPLA patients studied to date,¹⁻⁶ the analysis of (CAG)_n repeat number should serve as a highly accurate diagnostic and predictive test for this disease. At present, this test is useful to the physician seeking confirmation of a clinical diagnosis of DRPLA or when DRPLA is part of the differential diagnosis of a neurodegenerative or movement disorder. Of equal importance is the use of testing for predictive purposes. However, it must be stressed that its prognostic value is limited to modifying the *a priori* risk of inheriting a DRPLA allele. It does not provide any diagnostic information regarding the current status of the patient nor a prediction regarding age of onset of clinical symptoms. This latter point is extremely important as the association between (CAG)_n and age of onset in individual families may be variable.^{4-6,8} The following case report provides an illustration.

The pedigree is presented in fig 1. The relevant clinical histories of patients III·14, IV·26, and IV·27 and the methodology used to determine allele sizes have been described previously.⁵ IV·28, a 24 year old female who was recently evaluated, presented with a six year history of emotional lability, a generalised seizure disorder, mild ataxia, and dementia. Her mother's clinical course was that of a gradual mental deterioration and psychiatric disease (hallucinations and delusions), ataxia, and seizures over a nine year period. Her maternal grandfather (II·10) had an onset of psychiatric symptoms in his 20s and motor involvement in his early 30s. He was totally disabled by the age of 41. A seizure disorder was diagnosed at 53 years. He died at the age of 58. In general, there was an inverse correlation between (CAG)_n repeat number and age of onset among those family members tested.⁵ However, direct comparisons of DRPLA allele sizes from several

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Figure 1 Pedigree of DRPLA kindred.

family members emphasises the intrafamilial variability between repeat number and age of onset (fig 2). Variation in DRPLA allele size was small. At most, there was a change of four CAG repeats among these four patients, despite an age of onset that ranged from 33 in III·14 to 7 in IV·27 (age 21 in IV·26, 18 in IV·28). More striking was the demonstration of a similar number of repeats for III·14, IV·26, and IV·28 despite a 15 year difference in the onset

of ataxia and a 28 year difference in the onset of seizures, a unifying clinical feature in this family.⁵

What are the molecular diagnostic implications of this intrafamilial variability? Primarily it needs to be recognised that significant differences in age of onset can be associated with no, or minimal increase in repeat length^{4-6,8,9} and, as evident with the molecular genotyping of our family, very little prognostic information could have been inferred if the testing was predictive in nature. Furthermore, as the DNA used for such analyses is derived from leucocytes, it should be noted that tissue specific instability (somatic mosaicism) has been reported for this disorder.¹⁰ Therefore caution must be exercised in the interpretation of test results.

Second, like Huntington's disease, DRPLA is frequently associated with psychiatric symptoms⁹ which have been reported as the presenting feature in several families.¹¹ In our kindred, neuropsychiatric disturbances were common; III·18 was diagnosed as schizophrenic and his father II·10 carried a diagnosis of an organic brain syndrome with psychosis. III·14 suffered from visual and auditory hallucinations and III·20 and IV·28 were diagnosed with personality disorders. Anecdotally, both III·14 and IV·27 initially presented with subtle behavioural/personality alterations described as an inability to control their emotions. In summary, behavioural changes were the most common prodromal manifestation of the disorder in our family and should be recognised as a common clinical component of the DRPLA phenotype. This association does not, however, indicate that DRPLA gene testing should be offered to all patients with psychiatric disease as CAG expansions in the DRPLA gene have not been found in patients with a familial aggregation of psychoses or schizophrenia.^{12,13} Furthermore, given the high prevalence (1 to 5%) of psychiatric disease in the general population,¹⁴ a distinction should be made between using the molecular test for diagnostic purposes in a patient with psychiatric symptoms, family

Figure 2 Sequencing gel analysis of DRPLA alleles in affected family members. Methods were as described by Potter *et al.*⁵ All samples were run in duplicate. Repeat sizes (± 1 CAG repeat) were estimated by comparison to an M13 sequencing ladder. III·14 (allele sizes 15/65), IV·26 (13/65), IV·27 (16/69), IV·28 (8/65). The autoradiograph was slightly overexposed to enhance expanded alleles.

history, and unequivocal neurological findings (ataxia, choreiform movements, seizures, dementia) and in testing an otherwise "at risk" subject (that is, an a priori 50% risk for carrying an expanded allele) with only "soft behavioural signs" or psychiatric symptoms alone. In the latter case, testing should be considered predictive in nature with pre-test genetic counselling and a neurological examination recommended.

Third, despite the identification of the DRPLA specific (CAG)_n expansion mutation and the development of a highly accurate direct molecular diagnostic test for the disorder, the number of reported cases of DRPLA remains limited. In Japan, with a population of 120 million, the number of DRPLA patients and gene carriers is thought not to exceed 500 (M Yamada, personal communication) and elsewhere, current published reports include a total of seven DRPLA pedigrees^{3-6,15} with molecular data derived from only 29 subjects. Despite the demonstration of a common molecular defect in all DRPLA families studied to date, there have been clinical, molecular (that is, the degree of genetic anticipation), as well as neuropathological differences noted between Japanese, African-American, and European kindreds.^{4,5,9,15} Hence, it must be remembered that clinical correlations, particularly for cases of non-Japanese ancestry, are derived from a very small number of patients.

With the development of a direct DNA test, DRPLA joins HD, SCA-1, and Machado-Joseph disease (MJD/SCA-3), as examples of adult onset neurodegenerative diseases for which diagnostic and predictive testing is available. Direct gene testing for DRPLA is clearly useful to confirm or exclude a diagnosis in a patient with suggestive symptoms, particularly those with a family history of an autosomal dominant neurodegenerative disorder. However, given the significant inter/intrafamilial

phenotypic heterogeneity, variable age of onset, and prominent neuropsychiatric sequelae, it remains imperative that guidelines similar to those established for predictive testing for HD¹⁶ be used in testing for this rare neurodegenerative disorder.

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