DRPLA in Europe

Sir — Dentatorubropallidoluysian atrophy (DRPLA) is a neurodegenerative disorder generally defined by its distinctive pathology in the cerebellar and pallidal efferent outflow tracts. Most commonly seen in Japan, it is thought to be extremely rare in Europe. Most cases exhibit autosomal dominant inheritance although some are sporadic. Onset of symptoms ranges from childhood to late adult life, and the phenotype consists of a variable combination of seizures, dementia, ataxia, myoclonus and other movement disorders[1]. Recent studies in Japan have shown that DRPLA is associated with an expanded CAG trinucleotide repeat which maps to chromosome 12 (refs 2–4). The normal range of repeats, 7–23, was expanded to 49–75 repeats in DRPLA patients. A correlation between age of onset, severity and repeat size was observed. It was suggested that the repeat expanded mainly with paternal transmission and a putative "intermediate" allele was identified in the control population, possibly predisposing to the relatively high frequency of DRPLA in Japan[2]. Both of these features have been reported in Huntington's disease (HD)[5], which can clinically be confused with DRPLA.

We described recently the first reported kindred with DRPLA in the United Kingdom containing four affected individuals in two generations[6]. Diagnosis was made at autopsy in one patient. Age of onset of symptoms ranged from 15 to 38 years, and clinical findings included ataxia, dementia, chorea, dystonia and generalised seizures. We have now studied this family by amplification of the DRPLA CAG repeat (CTG-B37) using primers and conditions previously described[2]. The three living affected siblings had expanded alleles containing about 66–68 repeats (Fig. 1, lanes A–C). The small variation in repeat size between these siblings may be related to maternal transmission, although anticipation is apparent in this family with onset at 38 years in the mother (now dead) and 15–22 years in the offspring.

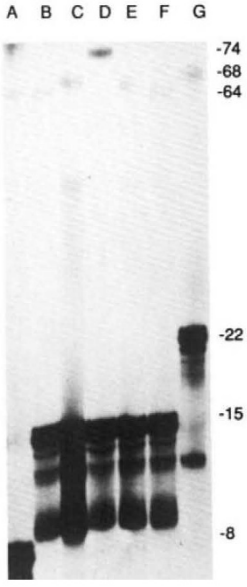

Fig. 1 Analysis of the PCR amplified products containing the CAG repeat in two DRPLA families. PCR products amplified with the CTG-B37 primers were analysed in a denaturing polyacrylamide gel. Individuals are identified by letters above each lane: lanes A–C contain samples from three affected sibs in the British family and lanes D–G affected members of the Maltese family. Sizes are estimated using a pGEM 32f(+) sequencing ladder, and repeat numbers indicated, but the presence of multiple bands makes precise sizing difficult.

We have also investigated a Maltese family with an autosomal dominant neurodegenerative disorder in which no diagnosis had been made. The age of onset ranged from 5–50 years, with a variable phenotype predominantly giving rise to dementia and seizures in younger patients, and ataxia with dementia, psychosis, chorea or myoclonus in older family members. Pathological features of DRPLA were not present in two autopsied patients; diagnoses considered were HD and inherited prion disease. However, the DRPLA expansion was also present in this kindred (range 64–74 repeats in affected subjects; Fig. 1). There was again anticipation, associated with paternal transmission; the expanded allele increased in size from 64 to 66 to 74 repeats when transmitted from grandfather (lane F) to father (E) to son (D), with increasingly early onset of symptoms.

In 35 unrelated Caucasian control subjects we found a repeat range of 7–24 (confirmed by cycle sequencing of representative alleles), with a bimodal distribution similar to that reported in a CEPH family and the Japanese controls[2,4]. No "intermediate" alleles (>30 repeats) were seen in our relatively small control series.

Our findings indicate that DRPLA in Europeans, while rare, can have the same molecular genetic basis as in Japan. This diagnosis should be considered in patients with any autosomal dominant disorder causing combinations of dementia, other psychiatric disorder, seizures, ataxia, dystonia, chorea, myoclonus or Parkinsonism, including those thought to have HD who do not have the HD CAG expansion. It will be interesting to establish the frequency of the DRPLA mutation in sporadic cases of currently obscure multisystem neurodegenerative disorders.

Thomas T. Warner
Lee Williams
Anita E. Harding
Neurogenetics Section,
University Department of Clinical Neurology,
Institute of Neurology,
London WC1N 3BG, UK

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Erratum

In the December issue of *Nature Genetics* (1993) the piece of correspondence entitled "Mild ALS in Japan associated with novel *SOD* mutation" appeared with M. Ogasawara as the first author. The authors would like M. Aoki, not M. Ogasawara, to be cited as first author in any future communication. □