Is DRPLA also linked to 14q?

Sir — Until now, the nosology and cause of dentatorubro-pallidoluysian atrophy (DRPLA) has been poorly understood[1]. DRPLA is an autosomal dominantly inherited neuropathogical entity characterized by various combinations of the following clinical symptoms: cerebellar ataxia, myoclonus, epilepsy, dementia and involuntary movements such as chorea and dystonia[1]. Choreic, ataxo-choreic and myoclonic-epileptic forms have been distinguished on the basis of this phenotypic diversity[2] although all three clinical pictures can be found in the same family[3].

Two clinically similar ataxic syndromes, Machado-Joseph disease (MJD)[4] and an autosomal dominant spinocerebellar ataxia (SCA3) (ref. 5) have been localized in the same region of chromosome 14q24.3–qter. Although clinical differences are found between the two diseases, allelic mutations at the same locus may be involved[5]. This prompted us to test the hypothesis that ataxic DRPLA is also linked to this locus.

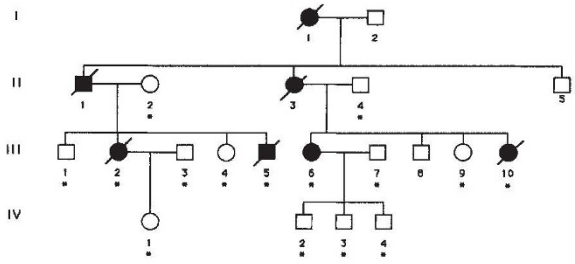

Fig. 1 Partial pedigree of the DRPLA family. Asterisks indicate sampled and tested individuals. (Individual II-3 was examined, but not genotyped.)

A six-generation French family with 11 affected individuals was studied. Five patients were examined (Fig. 1). Mean age at onset and disease duration were, 33 years (range 22–51) and 9 years (range 4–15). The clinical signs at onset were unsteady gait in three out of five patients, myoclonus in one and depression in another. All patients presented with mild cerebellar ataxia, moderate to severe dysarthria, pyramidal signs in the lower limbs and supranuclear ophthalmoplegia. Dystonia in upper limbs and neck were present in three and one patients, respectively. Severe amyotrophy was found in two patients with disease durations of 11 and 13 years. Parkinsonian signs were observed in three patients. MRI or CT scans showed cerebellar and brainstem atrophy in the three patients studied (II-3, III-5, III-6). Four patients died. Mean age at death was 47 years (range 40–68).

Pathological findings in patient III-2 were suggestive of DRPLA. Moderate to severe neuronal loss and astrocystic gliosis were found in the dentate nucleus, red nucleus, pallidum and subthalamic nucleus. There was "grumose degeneration" of the dentate nucleus, and a slight decrease in neuronal density in the pontine nuclei and substantia nigra. In contrast, neurons were spared in other structures (in particular, putamen, thalamus, caudate nucleus, cerebellar cortex, inferior olives and posterior columns). Both the clinical and neuropathological pattern in this family are those of the ataxo-choreic form of DRPLA[2].

Four of five examined patients and 11 non-affected family members were genotyped for linkage analysis. Linkage with loci SCA1 (6p23.05-24.2) and SCA2 (12q23-24.1) was initially excluded (data not shown). Positive lod scores were found for all microsatellite markers, spanning 17cM of the MJD/SCA3 region on chromosome 14q24.3–qter (table), reaching 2.41 and 2.43 for *D14S67* and *D14S48* at the same locus. The fact that *D14S48* is closely linked to the MJD locus[4] strongly suggests that the gene responsible for DRPLA in this family is located in the MJD/SCA3 region. This hypothesis was confirmed by the demonstration of linkage homogeneity (HOMOG program)[6] among two SCA3 families[5] and the DRPLA kindred, for markers *D14S48* and *D14S67*. The odds were 1.5×10^6 : 1 in favour of linkage to this locus. The conditional probability that the DRPLA family is linked ranged from 0.98 to 1, for a confidence interval of 95%, indicating that a DRPLA gene is located in the MJD/SCA3 region. We cannot exclude, however, the possibility that DRPLA is genetically heterogeneous.

Another gene containing an expanded, unstable CAG repeat that maps to chromosome 12p has been shown to be responsible for DRPLA in Japanese kindreds (this issue of *Nature Genetics*)[7,8]. As gene(s) responsible for MJD, SCA3 and DRPLA map(s) to the same chromosomal region, fine genetic mapping and identification of responsible gene(s) is necessary to determine whether the same gene is affected, and whether allelic heterogeneity explains clinical and neuropathological differences among these diseases.

Table Two-point lod scores for 14q24.3-qter markers in a DRPLA kindred

Markers	Recombination rates (θ)						
	0.00	0.01	0.05	0.1	0.2	0.3	0.4
D14S55	0.72	0.72	0.70	0.66	0.53	0.34	0.12
D14S48	2.43	2.39	2.21	1.97	1.46	0.90	0.33
D14S67	2.41	2.36	2.18	1.95	1.44	0.89	0.32
D14S81	0.22	0.21	0.18	0.15	0.08	0.03	0.00

Genotypes were determined by PCR and blotting[5]. Linkage analysis was performed with the MLINK program from the LINKAGE package (version 5.1). Age dependent penetrance was taken into account. Disease frequency was set at 0.0001.

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