expedited publication

Frontal lobe or 'nonspecific' dementias are genetically heterogeneous

A. Ashworth, BSc; J. Brown, MD; S. Gydesen, MD; S.A. Sorensen, MD; M.N. Rossor, MD; J. Hardy, PhD; and J. Collinge, MD

The degenerative dementias are among the most common of serious diseases. They follow a relentless progressive course and there are no effective treatments. Alzheimer's disease (AD) is the most common subtype, but many cases of degenerative dementias, perhaps 10%, lack the distinctive pathologic features that allow such histologic subclassification.[1] Such "nonspecific" dementias are highly familial,[1-3] with an autosomal dominant pattern of disease segregation; they frequently have clinical features of frontal lobe dysfunction. Recently, Wilhelmsen et al[4] assigned a gene for the disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) to chromosome 17q21-22, and suggested that other syndromes, including "dementias lacking specific histological features," may be allelic.

We have been studying a large kindred from the Jutland region of Denmark[5] that constitutes the largest published pedigree multiply affected by dementia in which affected individuals lack distinctive histopathologic features; 20 individuals have been affected in three generations with a pattern of disease segregation consistent with autosomal dominant transmission. Affected individuals in this family share clinical features with DDPAC, most notably disinhibition, dementia, and parkinsonism.[6] Amyotrophic lateral sclerosis is not present, but this feature occurred in only one case of DDPAC.[6] The age of onset is also higher (range, 50 to 67) than in DDPAC. Similarities in pathologic features include frontal lobe atrophy and the lack of amyloid deposition and neurofibrillary tangles.

We therefore studied the segregation of chromosome 17 markers in this large family with nonspecific dementia (table). Multipoint analysis using these markers gave location scores below −5 across the entire candidate region, excluding linkage of this family to the DDPAC locus on 17q21-22. Our finding establishes such familial nonspecific dementias to be genetically heterogeneous. Genetic linkage to another chromosome has now been established in this kindred.[7] The absence of definitive clinical or neuropathologic diagnostic criteria in these relatively common neurodegenerative diseases underlines the need for further molecular genetic studies both to allow their classification and to provide insights into their pathogenesis. The identification and characterization of the disease gene in this family and the 17q21-22 gene will add to the expanding list of genes known to cause dementia; such molecular markers will allow presymptomatic testing in appropriate kindreds, although incomplete penetrance and variable expressivity, if present, may complicate such applications. The identification of genes causing these types of dementias will ultimately allow differential diagnosis at the molecular level and enable their classification on etiologic criteria.

From the Department of Biochemistry and Molecular Genetics (Drs. Brown and Collinge, and A. Ashworth), Prion Disease Group, St. Mary's Hospital Medical School, Imperial College, London, UK; the Department of Medical Genetics (Drs. Gydesen and Sorensen), University of Copenhagen, Copenhagen, Denmark; the Department of Neurology (Drs. Rossor and Collinge), St. Mary's Hospital, London, UK; and the Departments of Psychiatry, Pharmacology, Neurology, and Biochemistry (Dr. Hardy), Suncoast Alzheimer's Disease Laboratories, University of South Florida, Tampa, FL.

Received April 17, 1995. Accepted in final form June 12, 1995.

Address correspondence and reprint requests to Dr. J. Collinge, Department of Biochemistry and Molecular Genetics, Prion Disease Group, St. Mary's Hospital Medical School, Imperial College, London W2 1PG, UK.

References

1. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch Gerontol Geriatr 1987;6:193-208.
2. Knopman DS, Mastri AR, Frey WH, Sung JH, Rustan T. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology 1990;40:251-256.
3. Neary D. Non Alzheimer's disease forms of cerebral atrophy. J Neurol Neurosurg Psychiatry 1990;53:929-931.
4. Wilhelmsen KC, Lynch T, Pavlou E, Higgins M, Nygaard TG. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. Am J Hum Genet 1994;55:1159-1165.
5. Gydesen S, Hagen S, Klinken L, Abelskov J, Sorensen SA. Neuropsychiatric studies in a family with presenile dementia different from Alzheimer and Pick disease. Acta Psychiatr Scand 1987;76:276-284.
6. Lynch T, Sano M, Marder KS, et al. Clinical characteristics of a family with chromosome 17-linked disinhibition-dementia-parkinsonism-amyotrophy complex. Neurology 1994;44:1878-1884.
7. Brown J, Ashworth A, Gydesen S, et al. Familial non-specific dementia maps to chromosome 3. Hum Mol Genet (in press). ■

Table. Pairwise lod scores

Locus	θ 0	0.05	0.1	0.15	0.20	0.25	Z_{max}	θ
D17S250	−4.21	−3.04	−1.93	−1.27	−0.08	−0.53	0.00	0.50
D17S787	−4.41	−2.46	−1.53	−1.00	−0.65	−0.41	0.00	0.50
D17S933	−4.14	−2.36	−1.50	−1.00	−0.66	−0.43	0.00	0.50
D17S953	−3.30	−1.40	−0.97	−0.69	−0.49	−0.34	0.00	0.50