Frontal lobe or "nonspecific" dementias are genetically heterogeneous.


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 nosologic subclassification. Such "nonspecific" dementias are highly familial, 1,2 with an autonomic dominant pattern of disease segregation, they frequently have clinical fea-
tures of frontal lobe dysfunction. Recently, Willemen et al. 3 identified a gene for the distribution-dementia-parkinsonism-
motor-neuropsychiatric complex (DDPAC) 17q21-22, and suggested that other syndromes, including "dementias lacking specific histological features," may be clinical.

We have been studying a large kindred from the Jutland region of Denmark 4 that constitutes the largest published pedig-
area 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 seg-
regation consistent with autosomal dominant transmission. Affected individuals in this family share clinical features with DDPAC, most notably disorientation, dementia, and parkinson-
isms. 5 Amyotrophic lateral sclerosis is not present, but this fea-
ture occurred in only one case of DDPAC. 6 The age of onset is also higher (50 to 69) 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 0 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 clin-
ic or neuropathologic diagnostic criteria in these relatively common neurodegenerative diseases underlines the need for fur-

ermore genetic studies both to allow their classification and to provide insights into their pathogenesis. The identifica-
tion and characteristics of the disease genes in this family and the 17q21-22 gene will add to the expanding list of genes known to cause dementias; such molecular markers will allow a more pre-

tomotic testing of 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 (O.A.; Brown and Collinge, and A. Ashworth); For Dementia Group, D. Mary's Hospital Medical School, Imperial College, London, U.K.; the Department of Medical Genetics (O. Gygi-BrSI and Sorenson); University of Copshagen, Copshagen, Denmark; the Department of Neurology (O. Brown and Collinge), St. Mary's Hospital, London, U.K.; and the Departments of Psychiatry, Pharmacology, Neurology, and Biochemistry, D. Mary's Hospital Mental Health Institutions, University of South Florida, Tampa, FL.

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Address correspondence and reprint requests to Dr. J. Collinge, Department of Biochemistry and Molecular Genetics, For Dementia Group, D. Mary's Hospital Medical School, Imperial College, London W2 1PG, U.K.

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5. Huygen S, Hoogen R, Wissenburg L, Alshapple T, Sorenson S. Neur-


Table: Pairwise lod scores

<table>
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<tr>
<th>Locus</th>
<th>0</th>
<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>Zmax</th>
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<tr>
<td>D17S260</td>
<td>-4.21</td>
<td>-3.84</td>
<td>-1.85</td>
<td>-1.27</td>
<td>-0.98</td>
<td>-0.53</td>
<td>0.00</td>
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<tr>
<td>D17S797</td>
<td>-4.41</td>
<td>-3.45</td>
<td>-1.52</td>
<td>-1.90</td>
<td>-0.85</td>
<td>-0.41</td>
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<tr>
<td>D17S883</td>
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<td>-2.85</td>
<td>-1.50</td>
<td>-1.60</td>
<td>-0.66</td>
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<tr>
<td>D17S891</td>
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<td>-0.97</td>
<td>-0.69</td>
<td>-0.49</td>
<td>-0.34</td>
<td>0.00</td>
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