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Frontotemporal Dementia Linked to Chromosome 3

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Abstract
A large pedigree with autosomal dominant frontotemporal dementia has been identified. Positional cloning has linked the disease gene to the pericentromeric region of chromosome 3. Clinical, neuropsychological, imaging, pathological and molecular genetic data are presented. The genetic mutation responsible for the disease has not been identified.

Introduction

We report on the results of a multinational, multidisciplinary study of a novel form of frontotemporal dementia (FTD) defined by its clinical, neuropsychological, imaging and pathological features and its linkage to the pericentromeric region of chromosome 3 (FTD-3).

FTD-3 has been described in a single pedigree, which originates and resides in western Jutland, Denmark. The family has been studied for over 15 years by Dr. Susanne Gydesen and more recently by our collaboration – FreJA (Frontotemporal Dementia Research in Jutland Association). The family was first described by Dr. Gydesen et al. in 1987 [1]. Information about the linkage to chromosome 3 was published in 1995 [2] and full clinical and pathological details and references to all earlier works on this topic issued in *Neurology* were published in 2002 [3] (with a supplement on the journal web site).

The Family

The proband was a farmer's wife who was born in 1876. She had 12 children who survived to adulthood. She developed dementia at the age of 56 years and died in 1948 at the age of 68 years. Eight of her children developed dementia and 1 further individual died in a traffic accident at the typical age of onset of this disease. He had passed the disease onto his children. Therefore, he must have carried the disease gene. It is possible that his accident was related to early dementia.

Twenty-six individuals in 4 generations developed dementia. There was male to male transmission and the pat-

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tern of inheritance was autosomal dominant. The age of onset varied between 46 and 65 years and the duration of the disease between 3 and 21 years. The mean age at disease onset was 57 years. In 1995 [2], we published evidence that there was anticipation of the age of onset with paternal transmission. However, recent paternally inherited cases have had a later onset than their father, casting doubt on our earlier observation.

There is a trend to increasing age of onset in more recent decades, suggesting the possibility of a protective factor, which is likely to be environmental. However, the trend is not statistically significant [FReJA, unpubl. obs.].

Clinical Characteristics

The clinical phenotype has been uniform, when the large number of cases is considered. The disease starts with a change in behaviour and personality. Affected individuals may become disinhibited or may withdraw and become apathetic. Ritualized behaviour, loss of emotion and change in eating habits are common. Some individuals develop dyscalculia, suggesting a parietal lobe involvement, but no individuals have early features such as route-finding problems or visuospatial problems. The disease is generally slowly progressive and the patient develops dynamic aphasia, which typically progresses to abbreviated words and then mutism.

Physical signs are absent in the early stages of the disease. After 4 or more years into the illness, several individuals have developed a striking motor syndrome. Many of these individuals have been exposed to neuroleptic drugs, but the syndrome continues to progress years after the neuroleptic drugs have been stopped. They develop an asymmetric akinetic rigid syndrome with arm and gait dystonia and pyramidal signs.

A retrospective structured interview of carers shows close similarity in symptoms to other cases of FTD [4] and clear differences to Alzheimer's disease. The results of these interviews indicate early behavioural and personality change with preservation of episodic memory and topographical orientation, as well as a lack of insight and empathy.

More detailed recent studies on affected individuals show very widespread cognitive deficits with preservation of memory and visuospatial skills. Monitoring of individuals using serial Mini-Mental State Examinations reveals relatively good scores early in the illness and then a sharp decline with worsening dynamic aphasia.

Nineteen affected individuals have had a CT brain scan. Four out of 5 with symptoms at the time of scanning showed global atrophy. One of the 14 without symptoms had atrophy; she developed symptoms of the disease 15 years later. On CT brain scans, the atrophy has a generalized pattern with both cortical and central atrophy having secondary enlargement of the lateral ventricles. There is no clear frontal preponderance. MRI scans have been performed in 2 cases showing a similar pattern of atrophy with some frontal preponderance and some white matter changes in 1 individual.

Positron emission tomography (PET) scanning measuring quantitative regional cerebral blood flow (rCBF) with 0–15 water has been performed in 4 affected individuals and 6 first-degree 'at risk' individuals. PET CBF scans of first-degree relatives were all considered to be within normal limits at the time of scanning. One of the healthy first-degree relatives was rescanned 6 years later after she had developed the disease. The new scan showed no significant changes in either the absolute CBF values or in the regional distribution of the flow. In the affected individuals, PET scanning showed a reduction in the perfusion of the frontal, temporal and parietal lobes, without clear frontal preponderance. Normal flow measurements were obtained in the primary visual cortex, thalami, basal ganglia and cerebellum. A visual comparison of the scans between the 4 patients indicates more pronounced deficits with lower rCBF values in the more severely affected patients.

Pathology and Genetics

Pathological examination of the brain has been performed in 6 individuals, but only 3 of these brains are still available for study. On external examination and slices, there is mild generalized, but mainly frontal, cortical atrophy with neuronal loss and gliosis, affecting particularly the upper half of the cortex. Some brains show mainly frontal white matter attenuation with mild gliosis and loss of myelin. There are no inclusion bodies and staining for beta amyloid and prion protein is negative. There is some tau deposition, more marked in individual 11,12 who had a very protracted disease course.

Molecular genetic studies published in 1995 [2] demonstrated a linkage of the disease gene in this family to the pericentromeric region of chromosome 3. Repeat analyses of newly affected individuals have confirmed the linkage to this region. Extensive sequencing of candidate genes in the region has not revealed a pathogenic mutation. Earlier

studies suggested that there was anticipation of the age of onset with paternal inheritance, which led to an extensive search for a trinucleotide expansion mutation; however, none has been located.

Southern blot analysis is being used to look for large genetic deletions and fluorescent in situ hybridization technology is being employed to identify larger chromosomal rearrangements.

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