CMLS, Cell. Mol. Life Sci. 54 (1998) 925–927
1420-682X/98/090925-03 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Chromosome 3-linked frontotemporal dementia

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Abstract. Frontotemporal dementia accounts for a significant minority of all cases of presenile dementia. Many pedigrees have been described in which frontotemporal dementia is inherited as an autosomal dominant trait. Frontotemporal dementia is genetically heterogeneous with loci identified on chromosome 17 and chromosome 3. Clinical, pathological and genetic findings are described in a large Danish family in which the disease gene lies in the pericentromeric region of chromosome 3.

Key words. Frontotemporal dementia; Pick's disease; chromosome 3.

The history of the nomenclature and classification of the frontotemporal dementias is complex and confusing. Earlier in this century most patients with progressive dementias with evidence of early frontal lobe or temporal lobe disease were diagnosed as cases of Pick's disease. In the last 20 years a number of alternative names have been, used, either stressing the frontal predominance of the disease or the lack of specific pathological features. A consensus statement in 1994 adopted the term 'frontotemporal' dementia [1] to describe these diseases; this term is now widely accepted.

Frontotemporal dementia (FTD) is now recognized as an important cause of cognitive decline. Patients with FTD present either with symptoms suggestive of frontal lobe dysfunction, such as personality change or disinhibited behaviour, or with symptoms suggestive of temporal lobe dysfunction, such as hyperorality. A few patients present with striking symptoms suggestive of focal cortical degeneration, such as progressive nonfluent aphasia or semantic dementia. Imaging the brain of patients with FTD usually reveals frontal lobe and/or temporal lobe atrophy. At postmortem examination, macroscopic inspection of the brain usually confirms that there is predominantly anterior atrophy. Microscopy may reveal the typical pathological changes of Pick's disease, motor neuron disease or other neurodegenerative diseases, but often shows neuronal loss and gliosis without specific pathological features.

Genetic factors have been recognized as important in FTD by most groups who have published series of cases. Three have suggested that about 50% of affected individuals have a first degree relative with dementia [2–4]. A number of pedigrees have been published in which FTD is inherited as an autosomal dominant trait [5–7]. Molecular genetic studies on these families have attempted to locate the genes responsible for FTD by positional cloning. The first report of genetic linkage in an FTD pedigree was to the long arm of chromosome 17 in 1994 [8]. A number of other groups have replicated this linkage in other pedigrees and have adopted the term 'FTD and parkinsonism linked to chromosome 17' to describe this disease [7]. Wilhelmsen reports on the latest findings in chromosome 17-linked FTD with parkinsonism in this issue. We reported linkage in 1995 to the pericentromeric region of chromosome 3 in a large dementia pedigree originating in Jutland, Denmark [9]. We originally used the term 'nonspecific dementia' to describe this pedigree, but the family fulfils the published criteria for FTD, and we have now adopted this term. This paper summarizes our findings in this pedigree.

The family

The family was first described by Susanne Gydesen in the 1987 [5]. The original affected individual was a

farmer's wife from western Jutland who was born in 1876 and developed a dementia at the age of 56 years. She died 12 years later in 1944. She had 12 children of whom 8 have developed a dementia; an additional child who died prior to the average age at onset of the disease carried the disease gene. The 9 'children' who carried the disease gene have also tended to have large families, and there are over 50 at-risk individuals in the third generation. Thirteen of these have now developed a dementia; many more individuals in this generation are at risk of developing the disease, and many of these are assessed annually. Many of these third generation 'at risk' individuals have children and grandchildren. In total, several hundred descendants of the original farmer's wife may carry the disease gene but are below the age of risk for developing the disease. An abbreviated pedigree is shown in figure 1.

Clinical features

The age at onset of the disease varies between 48 and 67 years, with a mean age of 57 years. Individuals who inherit the disease from their father develop symptoms significantly earlier (average 52 years) than individuals who inherit the disease from their mother (average 61 years). This difference in the age at onset between paternally and maternally inherited cases is statistically significant [9]. Affected individuals tend to present with personality change. Most become more apathetic, apparently losing interest in friends and hobbies, although some become disinhibited in their social behaviour. Some individuals have developed hyperorality, for example, eating excessive amounts of food or mouthing nonfood objects. Dyscalculia has been an occasional early feature; this may reflect parietal lobe or frontal lobe disease. As the disease progresses, the patients develop a nonfluent aphasia, and spontaneous speech becomes very sparse; eventually patients usually become mute. A number of affected individuals have developed parkinsonian features, but this is generally following treatment with neuroleptic drugs for behavioural problems. Withdrawal of the drug does not completely reverse the parkinsonian syndrome in the affected individual. Occasional patients who have had the disease for several years have developed pyramidal signs; a single individual has developed an arm dystonia. Terminally ill patients may have swallowing problems. No individual examined has developed evidence of lower motor neuron disease. None have had epileptic seizures. The clinical phenotype appears similar to that described in the chromosome 17-linked families, although the parkinsonian features are probably less common and milder than in some chromosome-17 linked pedigrees.

Neuroimaging typically shows generalized cerebral atrophy, sometimes with a frontal predominance. Electroencephalograms are typically normal early in the disease. Cytogenetic studies on a single, affected individual did not show any gross chromosomal abnormalities.

Pathological features

Five individuals have had postmortem examinations. Although we have the postmortem reports on these individuals, three of the brains have been lost or destroyed. All postmortem examinations have shown generalized cerebral atrophy which includes the frontal lobes. Microscopically in the cortex there is neuronal loss and gliosis, but no distinctive neuropathological features. One report mentioned some gliosis and white matter changes in the brainstem and cerebellum. There is no significant β-amyloid staining or prion protein staining in the brains examined.

Genetics

The pattern of inheritance is suggestive of autosomal dominant inheritance of the disease gene with high penetrance. Several individuals have developed the disease since the family was first reported, suggesting that

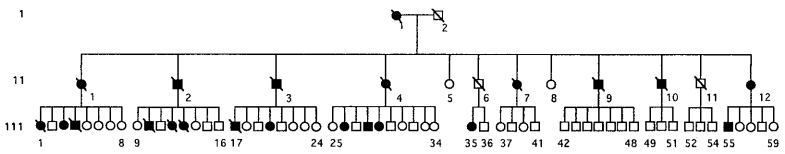

Figure 1. Abbreviated pedigree of the Jutland family.

the high penetrance of the disease gene in the family is not due solely to ascertainment bias. Individuals who have developed the disease, from their father have tended to be younger than those with maternal transmission of the disease suggesting that there is anticipation of the age at onset with paternal inheritance. This observation suggests that the disease might be produced by a trinucleotide expansion mutation. There are no other obvious phenotypic differences between paternally and maternally inherited cases.

We started genetic studies on the family in 1990 using genetic linkage techniques on genotypes generated using restriction fragment length polymorphisms. We switched to more highly polymorphic microsatellite markers when these were described. Initially, we concentrated on examining and excluding genes known to cause other familial dementias [10, 11], then we commenced a formal genome search and by 1994 we had excluded most of the genome. We established linkage to the pericentromeric region of chromosome 3 in 1994 with help from the facilities at Généthon, France [9]. The maximum multipoint lod score obtained was $+5.6$ adjacent to the marker D3S1552. A common 'disease chromosome' could be identified, shared by all the affected individuals, between the markers D3S1284 and D3S1603, a genetic distance of about 12 centimorgans (cM). Identification and typing of further affected individuals has reduced this area to about 4 cM; this remains a formidable physical area to analyse.

Current work

Although we have not found direct evidence that the disease in this pedigree is due to a trinucleotide expansion mutation, this remains a strong possibility, and we are identifying and typing trinucleotide expansions within the candidate region. There are no obvious candidate genes within the genetic area shared by all the affected individuals.

Annual assessments of the affected individuals and individuals with a high risk of developing the disease are performed and continue to identify new cases of the disease.

It is possible that the Jutland family will be the only chromosome 3-linked FTD family. It is more likely that other chromosome 3-linked FTD families will be identified. Identification of the causative genetic mutation is the priority in our future work. This will enable us to study how the genetic mutation leads to the dementia and provide insight into the pathogenesis of this important group of diseases.

Acknowledgements. Susanne Gydesen originally found the family and has jointly assessed all the affected and at-risk individuals. A number of individuals have helped with the laboratory work over the last few years, but recently the bulk of the laboratory work has been performed by Tony Ashworth with supervision from Lizzy Fisher and John Collinge.

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