Frontal temporal dementia: dissecting the aetiology and pathogenesis

Satisfactory classification of frontotemporal dementias (FTD) has always been difficult with historical schemes being based on clinical symptoms and on pathology (reviewed, Kertesz, 2005) and more recent proposals focused on genetics (Foster et al., 1997). Concordance between these schemes is imperfect and the situation further complicated by the growing realization that there is a clinical, pathological and aetiological overlap between amyotrophic lateral sclerosis (ALS) and FTD.

A milestone in our understanding of FTD occurred at a consensus conference where genetics groups pooled their data and realized that a large proportion of FTD families showed linkage to chromosome 17 around the tau (MAPT) locus (Foster et al., 1997). Many of these families had tau pathology (Spillantini et al., 1998), and mutations in tau were subsequently found in all tangle positive cases (Reed et al., 2001). Furthermore, there is a direct relationship between the type of tau mutation and the neuropathology found on autopsy: mutations at the splice junction of, or within, exon 10 of tau lead to the selective deposition of 4 repeat tau in neurons and glia. The pathological phenotype associated with mutations elsewhere in tau is less predictable with both typical neurofibrillary tangles (consisting of both 3 repeat and 4 repeat tau) and Pick bodies (consisting of 3 repeat tau) having being described (e.g. Bronner et al., 2005). The presence of tau deposits within glia is also variable in families with mutations outside of exon 10. This disease is now informally designated FTDP-17T.

Unexpectedly, a sizeable minority of families with FTD show linkage to the region of the tau locus on chromosome 17, but they have neither tau pathology on post-mortem examination nor mutations in tau on the genetic analysis. Unlikely as it may seem, it is now widely believed that there are two loci leading to FTD within a few megabases of each other on chromosome 17 (Rosso et al., 2001). Mackenzie and colleagues (page 853) and Van der Zee and colleagues (page 841) elaborate on this topic in this issue of Brain.

Both reports describe in detail two of these enigmatic FTD families linked to chromosome 17, but without tau mutations. This entity is now informally designated as FTDP-17U. Mackenzie and colleagues report the neuropathological findings of several members of a large kindred in which family members died of a dementing disease. Their histopathology consists of distinctive ubiquitin positive, tau negative inclusions (UBIs) and is similar to that reported in other families linked to the region without tau mutations. Interestingly, histopathologically this syndrome resembles some cases of ALS, and one member of the family reported by Mackenzie and colleagues also met clinical criteria for ALS. This suggests that there is a pathogenic relationship between FTDP-17U and some cases of ALS (Mackenzie and Feldman, 2005), analogous to the relationship between Parkinson’s disease and Lewy body dementia previously noted in families with α-synuclein mutations (Gwinn-Hardy et al., 2000; Zarranz et al., 2004). The UBI pathology also, superficially at least, resembles the neuronal pathology in inclusion body myopathy with Paget’s disease and frontotemporal Dementia (IBMPFD), which is caused by mutations in the valosin containing protein (VCP) gene (Watts et al., 2004; Schroder et al., 2005), suggesting that this disease may also be part of the same family showing a similar disease mechanism.

Van der Zee and colleagues also find that many cases of apparently sporadic cases of FTD in Belgium share a common chromosome 17 haplotype with the family in which they identified the linkage. This suggests that a significant proportion of sporadic disease in their catchment area shares the same genetic aetiology, namely an incompletely penetrant founder mutation. Such a scenario would resemble the identification of the common G2019S dardarin mutation in sporadic Parkinson’s disease (Gilks et al., 2005).

While the findings of Mackenzie and Van der Zee and their colleagues are clearly of importance to our understanding of FTD, their implication for ALS is more speculative. Recent clinical and pathological data indicate that ALS and FTD form part of a disease spectrum (Mackenzie and Feldman, 2005). Approximately 5% of ALS patients have clinically florid dementia (Mackenzie and Feldman, 2005) and about half of patients with ‘classical’ ALS have subtle frontal and temporal lobe impairment (Massman et al., 1996; Strong et al., 1999; Lomen-Hoerth et al., 2003). Furthermore, UBIs are a characteristic neuropathological finding in ALS patients without cognitive impairment, ALS patients with cognitive impairment, ALS–FTD patients and ‘pure’ FTD patients, but not in cases of ALS with SOD1 mutations. Given this overlap of ALS and FTD, it is possible that the route to neuronal death in these conditions is similar. In this issue of Brain, a new genetic linkage to chromosome 9p is reported by Caroline Vance and colleagues (page 868) (see also Morita et al., 2006), which may replace earlier reported linkages to chromosome 9q (Hosler et al., 2000) and 16q.
(Ruddy et al., 2003) for which no confirmatory linkages have been subsequently reported. Families reported to have these presumably erroneous linkages, including one of those now known to be linked to chromosome 9p, appear to share the same characteristic UBI pathology of the families reported by McKenzie and Van der Zee and their colleagues. Thus, there may well be a previously unrecognized pathway to neuronal death involving a failure of protein degradation, which underpins a considerable fraction of both FTD and ALS cases and which involves several genes including perhaps VCP and other, as yet uncharacterized, genes on chromosomes 17q and 9p: certainty about this conjecture will come only when the genes and mutations underlying these syndromes are elucidated and researchers can investigate their biochemical interrelationships, if any. The recent identification of CHMP2B (Skibinski et al., 2005), a protein involved in membrane trafficking, as the likely basis for nerve cell loss in the Danish kindred with chromosome 3 linked dementia may play into the same pathway since this mutation is also likely to lead to a failure of membrane protein degradation.

Thus, FTD is as complex from a genetic perspective as it is from pathological and clinical perspectives: nevertheless, as the three papers in this issue of Brain exemplify, we are making enormous progress in dissecting the aetiology of this distressing complex of diseases.

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