Frontotemporal lobar degeneration through loss of progranulin function

The striking clinical and pathological features of frontotemporal lobar degeneration (FTLD) have attracted much attention ever since Arnold Pick reported the first disease cases and Alois Alzheimer described the characteristic nerve cell inclusions of Pick’s disease. We now know that FTLD is a common cause of dementia, especially in the population below the age of 65 (Neary et al., 2005). Clinically, it encompasses cases of frontotemporal dementia (FTD), semantic dementia (SD) and primary progressive aphasia (PPA). Of these, FTD is the most common. It is characterized by progressive behavioural and personality disturbances, which evolve gradually into cognitive impairment and dementia. SD is characterized by a loss of conceptual knowledge, whereas in PPA progressive language impairment usually precedes the behavioural symptoms. In some patients, behavioural symptoms are also associated with a parkinsonian syndrome or with motor neuron disease (MND).

Pathologically, FTLD is characterized by the severe degeneration of frontal and/or temporal regions of the cerebral cortex. It can be divided into three broad subtypes, based on the presence of abnormal inclusions inside nerve cells. Filamentous cytoplasmic inclusions made of hyperphosphorylated tau protein characterize a proportion of cells. Filamentous cytoplasmic inclusions made of hyperphosphorylated tau protein characterize a proportion of cells with FTLD, including Pick’s disease (Spillantini et al., 1998). In recent years, it has become apparent that a substantial number of disease cases is characterized by the presence of tau-negative, ubiquitin-positive inclusions (FTLD-U) (Hodges et al., 2004). The third subtype, FTLD lacking distinctive histopathology, where abnormal inclusions are not observed, appears to be much less common than believed previously (Mackenzie et al., 2006a).

FTLD has a substantial genetic component, in that up to 40% of cases are inherited in a dominant manner (Rosso et al., 2003). Several disease loci and genes have been identified on chromosomes 3, 9, and 17. Mutations in the Tau gene on chromosome 17q21 cause a subset of familial cases, with the current total standing at 40 different mutations (Goedert and Jakes, 2005). Where analysed, filamentous tau inclusions are present in nerve cells or in both nerve cells and glia. Clinically, FTD predominates, with some Tau mutations causing also a parkinsonian syndrome (hence the naming of this condition as FTD and parkinsonism linked to chromosome 17 (FTDP-17)). In addition, phenocopies of progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick’s disease and MND have been described in some families with Tau mutations. FTDP-17 is caused by a gain of toxic function mechanism, similar to what happens in the most common neurodegenerative diseases, such as Alzheimer’s disease and Parkinson’s disease. In these diseases, dysfunction of the proteins (amyloid-β, tau and α-synuclein) that are deposited in the characteristic neuropathological lesions (plaques, tangles and Lewy bodies) is central to the neurodegenerative process.

Things appear to be different for FTLD-U. Mutations in p97 [also known as valosin-containing protein in mammals and cdc48p in yeast] on chromosome 9p21-p12, an AAA-type ATPase involved in endoplasmic reticulum-associated protein degradation through the ubiquitin-proteasome system, and mutations in CHMP2B (charged multivesicular body protein 2B) in the pericentromeric region of chromosome 3, a component of the endosomal sorting complex required for transport (ESCRT) III, give rise to FTLD-U through loss of function of the mutant allele (Watts et al., 2004; Skibinski et al., 2005). This is also the case of the most recently identified cause of FTLD-U, namely mutations in the Progranulin (PRGN) gene on chromosome 17q21 (1.5 Mb centromeric of Tau) (Baker et al., 2006; Cruts et al., 2006). Known mutations cause loss of function of the mutant allele and progranulin is not found in the ubiquitin-positive inclusions. By electron microscopy, the latter consist of abnormal filaments (Pirici et al., 2006). Although the first mutations were reported only four months ago, it is clear that PRGN constitutes a major FTLD locus. More than 20 different mutations have already been described. The new work also explains the existence of familial forms of FTLD that map to chromosome 17q21, but lack Tau mutations and tau deposits, while exhibiting tau-negative ubiquitin inclusions.

Progranulin (also known as acrogranin and epithelin precursor) is a 593 amino acid glycoprotein that is composed of 7.5 tandem repeats of a 12-cysteine granulin motif with the consensus sequence CX5–6CX3CCX2CCX6 CCXDXHCCPX4CX5–6C (Bhandari et al., 1992). It is expressed in many tissues, including the nervous system. Although the physiological function of progranulin is only incompletely understood, it probably functions as a secreted growth factor and may be involved in tumourigenesis (He and Bateman, 2003). Most PRGN mutations are nonsense, frameshift and splice-site mutations that are predicted to cause premature termination of the coding.
sequence, creating null alleles with the mutant RNAs being degraded by nonsense mediated decay. This issue of *Brain* contains five papers which build on the reports (Baker et al., 2006; Cruts et al., 2006; Mukherjee et al., 2006; Huey et al., 2006; Gass et al., 2006) describing the first PRGN mutations.

One paper (Mackenzie et al., 2006b) reports the neuropathology of 13 patients from 6 families with different nonsense, frameshift and splice-site mutations in PRGN. Ubiquitin-immunoreactive intranuclear inclusions with a lentiform shape in neocortex and striatum were the most characteristic feature. They were found less consistently in other brain regions. In addition, ubiquitin-immunoreactive cytoplasmic inclusions in nerve cell bodies and neurites were also present in a number of brain regions. Spinal cord motor neurons were ubiquitin-negative. The pathological inclusions were not stained by progranulin antibodies. The nature and distribution of the pathological changes were similar in each family, consistent with each mutation resulting in a loss of function of the mutant allele. This study suggests that the presence of ubiquitin-positive lentiform intranuclear inclusions in neocortex and striatum is indicative of FTLD-U caused by PRGN mutations. However, these lesions are not specific to this type of FTLD-U, since they have also been observed in cases with p97 mutations (Forman et al., 2006). A recent report has described the presence of ubiquitin-positive intranuclear inclusions in FTLD-U caused by CHMP2B mutations (Parkinson et al., 2006). It remains to be seen whether inclusions in this condition show a similar cellular and subcellular distribution. These findings raise the question whether one or more neurodegenerative pathways cause FTLD-U. This will depend on whether a single or more than one protein makes up the filamentous ubiquitinated inclusions. As in other inclusions, it appears likely that ubiquitin becomes attached to at least one other protein that is the major component of the inclusions.

Snowden et al. provide a comprehensive clinical, neuropsychological and pathological description of two families with different PRGN mutations. The proband of one family presented with FTD, whereas the proband of the second family exhibited PPA at the outset. However, clinical phenotypes within both families were heterogeneous, in support of FTD and PPA belonging to the same spectrum of diseases. Individuals from both families also developed parkinsonism as a late event. Masellis et al. describe a novel PRGN mutation in the splice-donor site 3′ of exon 7 [IVS7 + 1 G→A] in a family with a corticobasal syndrome, extending the clinical spectrum of FTLD-U caused by PRGN mutations (Masellis et al., 2006). By RT–PCR of white blood cell RNA, the mutant allele was not detected, indicating a loss of function effect of this mutation. A mutation in the preceding nucleotide [IVS7 - 1 G→C] has also been reported in a family with a corticobasal syndrome (Gass et al., 2006).

Two papers in this issue (Boeve et al., 2006; Pickering-Brown et al., 2006) revisit old ground. They serve to emphasize the need to exercise caution when reporting novel ‘mutations’ in inherited neurodegenerative diseases, especially when these do not fit easily into known mechanistic categories. A few years ago, a familial form of FTD was reported to be associated with the insertion of an arginine residue after codon 352 of *Presenilin-1* (PS1) (Tang-Wai et al., 2002). Functionally, this insertion had the opposite effect to the majority of PS1 mutations, in that it reduced amyloid-β production (Amtul et al., 2002). At the time, the neuropathology associated with this insertion was unknown. Boeve et al. now describe the presence of ubiquitin-positive intranuclear and cytoplasmic inclusions in the proband, as well as a splice-site mutation in PRGN that results in loss of function of the mutant allele. It follows that the arginine insertion after codon 352 of PS1 is not pathogenic. Pickering-Brown et al. report that the A239T change in Tau that they had reported previously in an individual with FTD lacking tau inclusions (Pickering-Brown et al., 2002) is not pathogenic, since a PRGN deletion mutation has now been found. They also show that the previously reported nucleotide change at position +29 in the intron following exon 10 of Tau (Stanford et al., 2003) is non-pathogenic. It had been identified in a family with FTD, where it segregated with disease. However, it has also been found in the control population with a frequency of about 1% (D’Souza et al., 1999; Stanford et al., 2003). At autopsy, tau-negative, ubiquitin-positive inclusions were present. The authors concluded that the +29 change caused FTD without leading to tau deposition (Stanford et al., 2003), something that had not been observed for bona fide Tau mutations. The presence of a nonsense mutation in PRGN in this family shows that the +29 change in Tau is a benign polymorphism. All pathogenic Tau mutations probably lead to the formation of filamentous tau inclusions.

Many years ago, at a time when nothing was known about the aetiology of Alzheimer’s disease, Parkinson’s disease, Pick’s disease or MND, it was believed that an age-related reduction in growth factors required for the development and maintenance of function of nerve cells could cause neurodegenerative disease. However, this hypothesis did not fare well in subsequent years. Things have now come full circle with the identification of PRGN mutations in FTLD-U. The presence of filamentous inclusions in FTLD-U is unexpected, insofar as they are usually associated with diseases caused through a gain of toxic function mechanism. It will be important to learn more about the function of progranulin, the nature of its receptor and the intracellular events following receptor activation. Provided it can be delivered safely and effectively, replacement of the missing progranulin protein is an obvious therapeutic strategy.
Together, mutations in Tau and in PRGN account for 50–60% of cases of familial FTLD, with mutations in p97 and CHMP2B being less common. None of these genes appear to be major FTD-MND loci. Recent work has mapped a locus for FTD-MND to the short arm of chromosome 9 (Morita et al., 2006; Vance et al., 2006). The identification of the causative gene defect is awaited with interest.

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References


