

**SCIENTIFIC COMMENTARY****Progranulin plasma levels in the diagnosis of frontotemporal dementia**

Not so long ago many neurologists were trained to believe that Pick's disease was rare and usually impossible to differentiate accurately from Alzheimer's disease. Through the persistent efforts of several research groups, especially in Lund (Sweden) and Manchester (UK), it became clear that this 'disease' is not rare and can frequently be distinguished from Alzheimer's disease (Brun *et al.*, 1994). Now, this entity is better described as frontotemporal dementia (FTD) or frontotemporal lobar degeneration based on the frequent occurrence of lobar atrophy involving frontal and/or temporal lobes (Snowden *et al.*, 1996). And rather than constituting a single disease, FTD represents a group of overlapping disorders having different pathogenic mechanisms, some, but not all, of which have been identified.

There are several different ways to subdivide the various types of FTD. One is to use clinical manifestations such as the behavioural or language variants (such as semantic dementia and many cases of primary progressive aphasia) and FTD associated with motor neuron disease. The second type of subdivision is made on the basis of neuropathological features. This would include FTD with tau deposits (so called tauopathies), FTD with tau-negative, ubiquitin-positive inclusions and corticobasal degeneration.

The third approach to division is genetic (Seelar *et al.*, 2008). Although numbers vary partly because of ascertainment bias, about 20–40% of persons with FTD have a positive family history of dementia. In the last decade, two entirely different genes have been discovered that each cause 5–10% of these familial cases. The first to be recognized was microtubule associated protein tau encoded on chromosome 17q. This finding made a sensible biological bridge to those forms of FTD associated with tau deposition. Screening for mutations in the tau gene is now clinically available and can provide important information for diagnostic and genetic counseling purposes. Mutations in 'tau' may change the splicing of the gene and/or microtubule function, but do not alter the actual levels of the protein in peripheral tissues. Thus, there is no specific peripheral biomarker to identify persons with mutations in tau.

The second and most recently discovered gene underlying some forms of FTD is also encoded on chromosome 17q and is

known as progranulin (*PGRN* or *GRN*). Mutations in progranulin are associated with the forms of FTD having tau-negative, ubiquitin-positive inclusions (Gijssels *et al.*, 2008; van Swieten *et al.*, 2008). However, these inclusions are not composed of progranulin but rather the protein TDP-43. Strangely, mutations in the gene (*TARBP*) coding for TDP-43 do not cause FTD, but are responsible for a rare form of familial amyotrophic lateral sclerosis (Sreedharan *et al.*, 2008; Van Deerlin *et al.*, 2008). The connections between mutations in *GRN* and the deposition of TDP-43 in some forms of FTD and motor neuron disease remain unexplained parts of the FTD puzzle.

Progranulin and its related granulin peptides have been associated with a range of biological functions including development, inflammation, tumourgenesis and possibly a neurotrophic function in brain (Van Damme *et al.*, 2008). Most importantly, essentially all of the pathogenic mutations in *GRN* have been shown to result in haplo-insufficiency of the protein. This is because the mutations usually produce a premature stop codon resulting in a truncated mRNA which then disappears through a process known as nonsense mediated decay. Since these are autosomal dominant conditions in which each person has a normal *GRN* gene and an abnormal mutated gene (heterozygote), the normal gene continues to make normal protein and the mutated gene makes none. Thus, one would expect about a 50% reduction in total *GRN* protein (i.e. haplo-insufficiency).

In this issue of 'Brain', Nicole Finch and colleagues (2008) from the Mayo Clinic have capitalized on this haplo-insufficiency phenomenon to measure progranulin levels in plasma, comparing FTD subjects with controls. The most important conclusion of their work is clear and unequivocal. Subjects with mutations in *GRN* all have significantly reduced levels of the protein in plasma. [Two other groups have made similar observations on smaller numbers of subjects (Coppola *et al.*, 2008; Ghidoni *et al.*, 2008).] Finch and colleagues also make the important point that one out of 72 cases with a working clinical diagnosis of early onset Alzheimer's disease was found to have a *GRN* mutation, thus changing the diagnosis to familial FTD. The immediate consequence of these studies should be the development of a relatively simple laboratory test of plasma to identify FTD

patients likely to have mutations in *GRN*. This would be best used as a screening procedure for patients with early onset dementia (<65 years). Those with a positive or borderline result could then have sequencing of the *GRN* gene to establish the exact mutation. Such a screening test would be a major advance in dementia diagnostics.

As always, many questions remain to be answered. What is the best cut-off threshold for normal versus abnormal levels of plasma progranulin? Why do many cases of FTD with *GRN* mutations have less than the expected 50% level of plasma GRN? Do all pathogenic mutations in *GRN* produce haplo-insufficiency or are there mutations that would be missed by a plasma GRN measurement? What is the biologic relationship between progranulin and TDP-43 deposition? Finally, what causes the other ~80% of FTD cases? Plasma progranulin measurements are an important step forward, but much work remains to be done.

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