■ Frontotemporal dementia and *progranulin* mutations

Spina et al. provide the results of a multidisciplinary study of three individuals with frontotemporal dementia (FTD) associated with a *progranulin* (*PGRN*) sequence variation. Two cases had a *PGRN* truncating mutation, a family history of FTD, and ubiquitin-positive neuronal intranuclear inclusions (NII). The third case had a *PGRN* missense mutation, a strong family history of amyotrophic lateral sclerosis, and absence of NII.

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■ Weft and warp: Molecular pathology and clinical genetics knit a fabric of neurodegeneration

Commentary by Paul G. Ince, MD, FRCPath

Disparate threads of clinical, pathologic, and genetic evidence weave a tapestry supporting a hypothesis based on neuropathologic observations. The common finding of ubiquitinated neuronal cytoplasmic inclusions (U-NCI) in cases of amyotrophic lateral sclerosis (ALS), ALS-dementia (ALS-D), and the majority of frontotemporal dementia cases (FTD-U) suggested that these syndromes occupied a clinicopathologic spectrum in which a single underlying disease process, defined by molecular pathology, gives rise to diverse clinical phenotypes.¹ The article by Spina et al. significantly increases the body of evidence that underpins this paradigm of neurodegeneration. Their work relates to FTD, but the principle is equally applicable in disorders characterized by tauopathy and α -synucleinopathy. The old concepts of diseases (such as Alzheimer, Parkinson, Pick) are better regarded as nodal clinicopathologic syndromes within disease spectra characterized by

specific proteinopathies. Much of the impetus behind this view comes from recent work in FTD and ALS.

The enigma of familial FTD linked to chromosome 17q21, but not related to tau gene mutations, was recently solved by the discovery of pathogenic mutations in the gene encoding progranulin (*PRGN*).² Molecular pathology had already shown that these cases lie in the U-NCI class of molecular pathology rather than the tauopathy seen in FTDP-17. This article shows that the clinical expression of *PRGN* mutations (probably arising through null mutations and haploinsufficiency) is diverse within individual families, ranging from FTD with absent motor manifestation to ALS with no overt behavioral, language, or cognitive syndrome. The story is enhanced by the recent identification of TDP-43 as the protein most likely forming the molecular basis for U-NCI in this class of disorders.³ The U-NCI of *PRGN*-FTD are immunoreactive

to this protein, in common with those of sporadic ALS and sporadic FTD-U. The genetic basis of other familial FTD cases with U-NCI has been elucidated and includes mutations in several genes (*CHMP2B*, *VAPB*). The clinical spectrum in these cases is also diverse and they show U-NCI immunoreactive for TDP-43. If the TDP-43 story proves durable, a common pathway of neurodegeneration in FTD and ALS converges from several distinct genetic causes and the numerically larger cohorts of apparently sporadic cases.

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