

Profile

Howard Feldman: master of dementia



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Throughout his career, Howard Feldman has contributed to the characterisation of the natural history of the dementias, but he has also been involved in clinical trials and research on biomarkers, including his work on melanotransferrin and within the Alzheimer's Disease Neuroimaging Initiative. More recently, he was part of a research team that showed that patients with frontotemporal dementia (FTD) who have ubiquitin-immunoreactive neuronal cytoplasmic inclusions (FTDU-17) had mutations in the progranulin gene, a finding that caused great excitement among molecular geneticists working on dementia. "A seminal contribution to that paper began with the recognition that there was a condition that causes FTD that was associated with a particular pathology—the intranuclear inclusions", recalls Feldman. "When we went back to our clinical material we discovered that it most often had an autosomal-dominant pattern of inheritance."

At that point, Feldman and his group did not have a research grant to pursue this discovery further. Together with his co-principal investigator Ian Mackenzie, resources were pooled from existing research accounts to hire a research coordinator to begin the onerous work of developing the pedigree and establishing the DNA samples for linkage and molecular analysis. "For 12 to 18 months I would see Caroline Lindholm our coordinator at a distance down a corridor. To be honest I wasn't sure what kind of progress we were making until she came to a research meeting and rolled out this 18 page pedigree that is ultimately the family that we found the gene on." It was around that time that Feldman's group started to collaborate with Mike Hutton's team at the Mayo Clinic in Jacksonville, which did the molecular genetics. "You can't underestimate how involved these things are—there was an enormous amount of fieldwork to be done to gather all the information on all the relatives before we could even start sequencing genes", he says.

Virginia Lee, who works at the University of Pennsylvania, then contacted Mackenzie and Feldman to ask for access to the bank of tissue samples from patients with FTD that the University of British Columbia had built up over the years. Lee was able to identify the protein within the intranuclear inclusions as TDP-43. "That finding had even broader implications—identifying a proteinopathy that is behind FTD and amyotrophic lateral sclerosis", says Feldman, who is very proud of the work he has done to help these patients. "FTD is a nasty condition. To have an illness that runs through your family at a 50% rate and neither have a clear understanding of what it is nor anything about what

causes it, is really distressing." The next step is to try to work out what role progranulin has in FTD and whether it is linked in some way to the TDP-43 intranuclear inclusions.

Howard Feldman's route into medicine was somewhat unusual. His undergraduate degree was in English literature which, he says, taught him a great deal about human nature. But during this time he also became fascinated by the biology of the human brain and how it can malfunction, so he retrained in medicine. After qualifying, Feldman spent a few years working in general practice doing rural medicine. "That was very challenging", he says, "but I didn't have the sense of mastery that I wanted over the content and skills. I preferred the idea of trying to be a master in a specific area." So Feldman decided to specialise in neurology, with a particular emphasis on the cognitive disorders of dementia.

"Neurology ultimately reflects the extraordinary blend of understanding human nature, mind, emotion, cognition, all within the set of skills that allow you to evaluate and treat people for various conditions", says Feldman. So combining his interest in the humanities with a career in medicine seemed like a perfectly natural thing to do. But Feldman also notes that it wasn't until he started writing scientific papers that he became completely at ease with his new career. "I didn't find the sense of wellbeing and belonging, the sense that I was doing the right thing, until I started to have an active focus on writing", he says. In particular, he enjoys developing his thoughts and ideas about concepts of dementia into research grants or papers.

Feldman believes very strongly in doing research that helps the treatment of patients in the clinic. He is the director of the University of British Columbia Hospital's dementia clinic, which evaluates and treats upwards of 1200 patients each year; the clinic is engaged in a wide variety of research projects within the degenerative dementias. "A number of issues come up from going to clinics and understanding patients' unmet needs and understanding the enormity of the problems that they're dealing with", he says. "We have to work very diligently at the mantra of prevention. Within an ageing western society if we can delay the onset of dementia by 1 year we can reduce the prevalence by 10% over three decades. And if we delay it by 5 years we can reduce the prevalence by 50%. A lot of the things that we're working on fit into that kind of algorithm."

James Butcher
james@two-cultures.com

For more on the identification of TDP-43 within intranuclear inclusions see *Science* 2006; 314: 130–33