

Diagnosing pre-clinical dementia: the NZ Genetic Frontotemporal Dementia Study (FTDGeNZ)

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Imagine discovering you have dementia only to be told it could have been prevented if you knew 10 years earlier that you were at risk. The pathological processes of dementia begin decades before clinical symptoms arise¹ so by the time dementia is diagnosed clinically, cell death in specific brain regions can be extensive and the damage is likely irreversible.² Although no confirmed treatments currently exist, significant research efforts are currently focused on identifying disease-modifying therapies. When treatments are identified, pre-clinical diagnosis will be critical before irreversible changes have occurred in the brain. Towards understanding pre-clinical biomarkers of dementia, New Zealand researchers and clinicians are studying an aggressive form of dementia that has an identified genetic cause and a much more predictable course than sporadic Alzheimer's disease. The NZ Genetic Frontotemporal Dementia Study (FTDGeNZ) is a multidisciplinary, inter-institutional initiative in search of pre-clinical diagnostic markers of dementia in a large New Zealand kindred. The family carries a genetic mutation in the *MAPT* gene that predictably causes behavioural variant frontotemporal dementia (bvFTD).

FTD is a leading cause of early-onset dementia, typically striking between age 45 and 65. Large-scale epidemiological studies of FTD are lacking, but two groups have reported a prevalence of 15 per 100,000 45–64 year-olds in the UK.^{3,4} There are currently no prevalence data for New Zealand. Typically FTD is described as having two variants based on clinical

presentation—a language variant and a behavioural variant (bvFTD). Within the language variant two subtypes are recognised: non-fluent primary progressive aphasia (a disorder primarily of expressive language) and semantic dementia (a multimodal loss of semantic knowledge). BvFTD is characterised clinically by personality and behavioural change, impairment of social cognition and/or executive function deficits.⁵ Recent findings have suggested that variable memory difficulties are evident in bvFTD.⁶ Parkinsonism, usually without resting tremor, can be a feature of bvFTD. A minority of pathologically confirmed cases of bvFTD have been misdiagnosed as Alzheimer's disease, Parkinson's disease, corticobasal syndrome or progressive supranuclear palsy. Initial symptom onset is gradual, eventually progressing to severe generalised dementia. Average survival varies widely, ranging from 2–14 years, and differs by subtype. As with other progressive dementias there is currently no effective treatment; however, selective serotonin reuptake inhibitors and atypical antipsychotics can help with behavioural symptoms.⁷ The available data do not support the use of Alzheimer's disease drugs such as Memantine and acetylcholinesterase inhibitors.⁷ Parkinsonism typically does not respond to dopaminergic medications such as levodopa.⁷

The FTDGeNZ cohort consists of a single family (NZ-1) with familial bvFTD caused by an autosomal dominant mutation in the gene that encodes the protein tau (*MAPT*). Studying healthy mutation-carriers in this

family before clinical symptoms arise will allow measurement of potential biomarkers up to 30 years before expected clinical onset. The NZ-1 kindred provides a rare opportunity to study the earliest effects of a single mutation in environmentally and genetically similar participants, compared to related non-carrier controls. The mutation (*MAPT* 10+16 C>T) has been identified in 27 other families worldwide, which may constitute a single pedigree from a founder in North Wales.⁸ The mutation has complete penetrance, with an average age of onset of 50, although this is variable even within families.⁹ This mutation, like all *MAPT* mutations, leads to tau aggregation, neuronal dysfunction and cortical atrophy.

Like Alzheimer's disease, FTD is a prote-inopathy. It is defined pathologically by abnormal protein inclusions in neurons and/or glia that are associated with progressive dysfunction and cell death in frontal and/or temporal lobes. The inclusions usually consist of the proteins tau (~40%) or TDP-43 (~50%).¹⁰ FTD is distinguished from Alzheimer's disease pathologically by the distribution of tau inclusions and the relative absence of amyloid plaques. The relationship between pathology and phenotype is complex: there are correlations between the type of protein inclusion and the FTD subtype, but these are not exact.¹⁰ In 25–50% of cases these protein inclusions are caused by an inherited genetic mutation (familial FTD); the remaining cases are sporadic.^{11,12} Familial FTD is caused by a mutation in one of nine genes, most commonly *C9orf72*, *MAPT* or *GRN*. Familial and sporadic FTD of the same subtype are clinically indistinguishable.¹³

The aim of FTDeNZ is to identify accurate markers of disease onset, risk and progression that are relevant to both familial and sporadic FTD. The focus is on non-invasive, cost-effective diagnostic markers, in the hope that they will ultimately be used widely as a screening tool. Understanding the natural course of

FTD may also elucidate the pathological processes underlying related dementias. This is the only study of its kind in New Zealand and one of the largest pre-clinical studies of a family cohort with a single mutation internationally.¹⁴

We have enrolled 24 healthy participants from the NZ-1 kindred, ranging from 26–59 years old, and have undertaken baseline assessments measuring a range of potential biomarkers that are expected to be affected early in the disease course: blood-based molecules, olfactory dysfunction, cognitive dysfunction, mood changes, retinal changes, and structural and functional brain changes. These assessments will be repeated annually to track the earliest pathological changes that are associated with pre-clinical FTD in mutation carriers versus non-carrier controls.

In addition to identifying markers of pre-clinical dementia, FTDeNZ aims to assist and advocate for the dementia community in New Zealand, specifically those with FTD and other rare dementias. FTDeNZ works in close association with the Dementia Prevention Research Clinics to support the NZ-1 kindred. FTDeNZ is also willing to help clinicians, care-workers, carers and those with FTD connect with support networks, services and researchers nationally and internationally to advance early detection and treatment of dementia.

Support for FTD sufferers and their families is provided by Alzheimer's New Zealand. International resources for FTD and rare dementias are available, for example ftdtalk.org, ftdsupportforum.com, raredementiasupport.org and youngdementiauk.org. For those with suspected familial FTD, genetic counselling and genetic testing are provided by Genetic Health Service New Zealand. The International Society for Frontotemporal Dementias hosts a biannual meeting (the International Conference on FTD, ICFTD) to present research findings and provides workshops for caregivers and clinicians.

Competing interests:

Nil.

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