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Global Perspectives

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GENETICS OF FRONTOTEMPORAL DEMENTIA IN ASIA: ADVANCING KNOWLEDGE THROUGH COLLABORATION

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder characterized by selective involvement of the frontal and temporal lobes, where non-Alzheimer disease (AD) pathology is expected. FTD encompasses 3 distinct clinical syndromes including behavioral variant FTD (bvFTD) characterized by prominent behavioral abnormalities, and 2 language variants (semantic variant and nonfluent variant) collectively known as primary progressive aphasia (PPA). The most common FTD subtype, bvFTD, may manifest with disinhibition, compulsive/perseverative behavior, overeating, apathy, and emotional blunting. FTD is known in Western populations to be the second most common cause of dementia in those younger than 65 years.[1] In Asian populations, FTD appears to be far less common, being the third most common cause of young-onset dementia in some cohorts behind AD and vascular dementia.[2] The proportion of Asian patients with FTD who have a positive family history ranges from 9.5% to 20%,[2–4] considerably lower than the 30% to 50% seen in Caucasian populations.[5]

Since the discovery of the *C9orf72* hexanucleotide repeat expansion in 2011[e1] as a major cause of familial FTD, amyotrophic lateral sclerosis (ALS), and FTD-ALS syndrome, a few Asian cohorts, mainly in East Asia, have been screened for this expansion. Majounie et al.[e2] first identified 3 Asian carriers (1 familial ALS, 2 familial FTD), in the Japanese population; the repeat expansion has been found to account for 2.8% (3/109) of familial ALS, 0.4% (4/891) of sporadic ALS, and 0% (0/377) of normal healthy controls.[e3] Jiao et al.[e4] reported the first known *C9orf72* carriers in mainland China in a family with FTD-ALS (proband plus 2 presymptomatic siblings) and a patient with sporadic FTD out of 128 patients (3%). In Taiwan, the *C9orf72* mutation has been reported in 18.2% (4/22) of familial ALS and 2.0% (2/102) of sporadic ALS cases.[e5] Large *C9orf72* repeat expansions were also detected in 3 related Taiwanese patients with FTD, but not in other cohorts with various parkinsonian and cerebellar ataxia syndromes.[e6,e7] In Singapore, 2 unrelated Han Chinese families with an FTD-ALS phenotype carrying the *C9orf72* mutation have been identified so far, accounting for 3.7% of the FTD spectrum cases.[e8] Other Asian cohorts of patients with FTD have been screened and found to be negative for *C9orf72* repeat expansions.[e9,e10] In total, 25 *C9orf72* carriers have been reported in Asian patients (8 familial ALS, 6 sporadic ALS, 5 familial FTD, 1 sporadic FTD, 3 FTD-ALS, and 2 presymptomatic siblings), with clinical presentations appearing similar to those of Caucasian patients. However, given the small numbers reported at present, any potential phenotypic differences remain to be determined. This contrasts with data from studies in Western cohorts that report the frequency of *C9orf72* expansions to account for approximately 25% of familial FTD, 6% of sporadic FTD, 40% of familial ALS, 3% to 19% of sporadic ALS, and 30% of FTD-ALS cases.[e1,e2,e11] All reported Asian carriers have so far been shown to possess a similar risk haplotype to that of the hypothesized Scandinavian founder, suggesting a common founder effect that spread from Northern Europe to East Asia in human migration history. This vast geographical distance, however, prompts consideration that other hypotheses such as that of a predisposing haplotype generating multiple mutations may be viable.[e12] The only reported neuropathologic findings of Asian patients carrying the *C9orf72* mutation appear to be indistinguishable from those of Caucasian patients.[e13]

In general, mutations in the microtubule-associated protein tau (*MAPT*) gene and progranulin (*GRN*) gene account for 2%–11% and 5%–11% of familial FTD cases, respectively.[5] A systematic review and meta-analysis of Japanese familial dementias including FTD with parkinsonism linked to chromosome 17 identified 16 *MAPT* mutations in 84 patients (19%) and 2 *GRN* mutations in patients with PPA and FTD.[e14] In this meta-analysis, *MAPT*-positive patients appeared to possess clinical phenotypes not dissimilar to their Caucasian counterparts—with predominant FTD or AD-like presentations (prominent episodic memory loss), including 6 patients with early-onset progressive supranuclear palsy (PSP) in their 40s and

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From the National Neuroscience Institute, Singapore.

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eye movement abnormalities atypical for sporadic PSP.[e10,e14] Mean age at onset of *MAPT* carriers also appeared similar to other ethnic groups, at 45 ± 10 years.[e14] In a South Indian cohort, no pathogenic mutations or haplotypic association with disease risk in FTD, PSP, and corticobasal syndrome were found, suggesting that there may be other genetic or epigenetic factors contributing to the pathogenesis of FTD in the South Indian population.[e15]

Valosin containing protein (*VCP*) mutations have been reported in 12 East Asian patients, including 5 related individuals in China who were found to have a novel missense mutation in exon 3 on whole-exome sequencing presenting with Paget disease of bone but no evidence of FTD, 3 members of a Korean family presenting with inclusion body myositis with Paget disease of bone and FTD (IBMPFD), and one Japanese patient with sporadic ALS but without clinical FTD.[e16–e18] Of note, the Korean pedigree had a typical IBMPFD presentation, but atypical imaging features of asymmetric anterolateral temporal and inferior parietal atrophy, possibly broadening the phenotypic spectrum of *VCP*-associated FTD.[e16]

While this summarizes the current knowledge of genetic FTD in Asia (particularly East Asia), questions remain as to why Asian cohorts seemingly have a lower prevalence of FTD and positive family history of FTD. This apparent "lower" prevalence is likely related to underreporting by families, and it is possible that cultural factors have a large role in this. Frequently, changes in personality and behavior are not naturally associated with a disease state, but rather mistakenly attributed to the person's character. This results in patients presenting to medical attention late, usually when memory and language impairment set in and have advanced toward a dementia stage, or when abnormal behavior becomes too distressing for the family. Patients with PPA often present at a stage severe enough to render the patient nearly mute and neuropsychological assessment highly challenging. This is likely to be pervasive in rural parts of developing Asian countries, but is also highly common in cosmopolitan cities of developed Asian nations. More effort needs to be made to increase public awareness of young-onset dementias such as FTD and early-onset AD in Asia, so that families recognize the disease state and appropriate medical care can be started at an earlier stage when interventions still make some difference.

Many of the Asian patients with genetic FTD published in the literature have been seen in neurologic clinics, which by nature results in publication bias to a certain extent. This suggests more importantly that apart from the general public, it is vital to raise awareness of FTD among nonneurologists—including psychiatrists, internists, and geriatricians, all of whom will likely encounter FTD-related disorders in their practice. Such patients are frequently misdiagnosed as having psychiatric illnesses such as mid- or late-life bipolar disorder and schizophrenia, preventing them from accessing governmental resources and provisions for dementia care, including access to dementia day care facilities and nursing homes. Insurance policies almost never make provision for psychiatric illness. The apathy and inertia of bvFTD is often mistaken for moderately severe depression in the elderly, although this is a lesser issue given that treatment with selective serotonin receptor inhibitors for depression is also the mainstay of treatment for bvFTD. More concerning is that misdiagnosis is frequently accompanied by overprescription of antipsychotics to control behavioral symptoms, thereby contributing to the already impaired cognitive state and extrapyramidal side effects, and eventually hastening functional and cognitive decline.

On a broader scale, there is a crucial need for greater multinational efforts in collaboration among Asian countries, not only in education, but particularly regarding genetic screening in FTD and other dementias. The Asian genetic make-up is likely to differ from that of Caucasians; genetic factors and modifiers prevalent in Caucasian populations may have a weaker role in Asian cohorts. Whether this is related to weaker ascertainment or because Asian patients with FTD have genetic underpinnings unique from those of Caucasians remains to be determined. The only way to do so is with large-scale collaborations similar to those that are already commonplace among Western academic centers and that have brought about remarkable discoveries in the last few years in the field of genetic FTD.

Dementia is already an epidemic in Asia. The latest Alzheimer's Disease International report published in November 2014 showed that the number of persons in the Asia-Pacific Region with dementia will likely increase from 23 million this year to more than 70 million in the next 3 decades, accounting for more than half of the people with dementia worldwide (World Alzheimer Report, 2014). While AD and vascular dementia will likely account for much of the increasing incidence of dementia in Asia given the high prevalence of cardiovascular risk factors, it is very likely that with greater awareness, the proportion of patients with FTD will also increase significantly. Research into potential treatments for FTD, including compounds targeting tau and antisense oligonucleotide therapy for C9-related disease, is already under way in many centers around the world. Much research is also ongoing in presymptomatic genetic FTD carriers that will aid in developing biomarkers for use in preventative and therapeutic treatment trials. All that remains for Asia is the promise that when

such therapies do become available in the not-too-distant future, it will not be left too far behind.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The author reports no disclosure relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2015;85;2060-2062 Published Online before print October 2, 2015
DOI 10.1212/WNL.0000000000002045