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RESEARCH ARTICLE

C9orf72 expansions are the most common cause of genetic frontotemporal dementia in a Southeast Asian cohort

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Abstract

Objective: Frontotemporal dementia (FTD) encompasses a spectrum of neurodegenerative disorders, including behavioural variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA) and non-fluent variant PPA (nfvPPA). While a strong genetic component is implicated in FTD, genetic FTD in Asia is less frequently reported. We aimed to investigate the frequency of Southeast Asian FTD patients harbouring known genetic FTD variants. **Methods**: A total of 60 FTD-spectrum patients (25 familial and 35 sporadic) from Singapore and the Philippines were included. All underwent next-generation sequencing and repeat-primed PCR for *C9orf72* expansion testing. Neurofilament light chain (NfL) levels were measured in a subset of patients. **Results**: Overall, 26.6% (16/60 cases) carried pathogenic or likely pathogenic variants in a FTD-related gene, including: *MAPT* Gln351Arg (n = 1); *GRN* Cys92Ter (n = 1), Ser301Ter (n = 2), c.462 + 1G > C (n = 1); *C9orf72* expansion (35–70 repeats; n = 8); *TREM2* Arg47Cys (n = 1); and *OPTN* frameshift insertion (n = 2). Genetic mutations accounted for 48% (12/25) of patients with familial FTD, and 11.4% (4/35) of patients with sporadic FTD. *C9orf72* repeat expansions were the most common genetic mutation (13.3%, 8/60), followed by *GRN* (6.7%, 4/60) variants. Within mutation carriers, plasma NfL was highest in a *C9orf72* expansion carrier, and CSF NfL was highest in a *GRN* splice variant carrier. **Interpretation**: In our cohort, genetic mutations are present in one-quarter of FTD-spectrum cases, and up to half of those with family history. Our findings highlight the importance of wider implementation of genetic testing in FTD patients from Southeast Asia.

Introduction

Frontotemporal dementia (FTD) encompasses a heterogeneous spectrum of neurodegenerative disorders characterised by progressive impairment in behaviour, language and/or executive function, related to predominant atrophy in the frontal and temporal cortices.[1] Broadly, it can be categorised into three clinical subtypes – the most common behavioural variant FTD (bvFTD)[2] subtype, and the two language subtypes of semantic variant primary progressive aphasia (svPPA) and non-fluent variant primary progressive aphasia (nfvPPA).[3] FTD may coexist with amyotrophic lateral sclerosis in a syndrome termed FTD-ALS, as well as in Parkinsonian-like FTD syndromes. A strong genetic component has been implicated in FTD, with western European and North American cohorts

reporting a positive family history in 30–50% of FTD patients,[4] and a clear autosomal dominant pattern of inheritance in 10% of patients.[5] Studies conducted in Caucasian cohorts have found that approximately 60% of familial FTD patients are associated with mutations in microtubule-associated protein tau (*MAPT*), progranulin (*GRN*) and hexanucleotide expansion repeats in the open reading frame of chromosome 9 (*C9orf72*),[6] with *C9orf72* mutations being most common.[7] Less common mutations (<5%) seen in FTD include those in valosin-containing protein (*VCP*),[8] TARDNA-binding protein 43 encoding (*TARDBP*),[9] Tank-Binding Kinase 1 (*TBK1*),[10] Sequestosome 1 (*SQSTM1*),[11] Charged Multivesicular Body Protein 2B (*CHMP2B*),[12] Fused in Sarcoma (*FUS*),[13] and Ubiquilin-2 (UBQLN2).[14]

In contrast, fewer Asian FTD patients have a known genetic cause, with an international multicentre study showing only 9.5–20% of FTD patients reporting a positive family history.[15,16] Reports on the clinical and genetic characterisation of FTD amongst Southeast Asian countries are less studied. Our group previously described the demographics, cognitive symptoms, and longitudinal follow-up profiles of a cohort of 44 Southeast Asian FTD patients in comparison to Western cohorts.[17] A subsequent study by our group screened 52 FTD-spectrum patients (including atypical Parkinson's disease/progressive supranuclear palsy (PSP) patients) in Singapore and the Philippines for FTD-associated genes, and identified a homozygous *TREM2* R47C mutation in a patient with bvFTD,[18] along with reports of *GRN* mutation carriers in PPA patients from the Philippines.

In this study, we aimed to further define the clinicogenetic spectrum of FTD patients in Southeast Asia in a larger combined cohort (including 34 patients published previously[18]) of FTD-spectrum patients from Singapore and the Philippines using next-generation sequencing and *C9orf72* repeat expansion analysis. Levels of neurofilament light chain (NfL), a marker of axonal degeneration, were also examined in a subset of patients given its association with disease severity and mutation status in FTD.[19,20]

Methods

Patient recruitment

A total of 60 FTD-spectrum patients, comprising 38 bvFTD, 4 svPPA, 16 nfvPPA/indeterminate PPA, 1 FTD-ALS and 1 undetermined psychiatric diagnosis patients were included in this study. These patients were recruited between January 2015 and Aug 2021 from two tertiary neurological centres with specialist neurocognitive clinics - 45 from the National Neuroscience Institute, Singapore and 15 from the St Luke's Hospital, Philippines. Patients were recruited for research and underwent genetic screening if they had a family history of Parkinsonism, dementia or FTD, were of young-onset, or had additional overlapping clinical features such as FTD with Parkinsonism and/or ALS. The diagnoses of bvFTD,[2] svPPA,[3] and nfvPPA[3] were made by cognitive neurologists specialising in FTD according to international clinical criteria. As a significant proportion of PPA patients presented to the clinics at more advanced and nearly mute stages rendering classification difficult by their physicians, they were classified as nfvPPA/indeterminate PPA in this study (n = 16). Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) patients were not included in this study and will be reported separately. All patients and their families provided consent. Ethics approval was obtained from Singapore Health Services Centralised Institutional Review Board and St. Luke's Medical Centre Institutional Ethics Review Committee. A subset of patients included in the current updated cohort were previously published.[18,21]

Clinical evaluation

Clinical evaluations were performed by cognitive neurologists and global cognitive was evaluated using the Mini-Mental State Examination (MMSE)[22] or Montreal Cognitive Examination (MoCA).[23] Neuropsychological assessments scores were obtained if available. Disease severity was assessed using the Clinical Dementia Rating sum of boxes (CDR-SOB)[24] and the FTLD-modified Clinical Dementia Rating[25] score (FTLD-CDR, where available). Cerebrospinal fluid (CSF) was collected for measurement of Alzheimer's disease (AD)-related biomarkers as well as neurofilament light chain (NfL) levels in a subset of patients (n = 14) able to undergo lumbar puncture. Blood samples (n = 30) were collected for measurement of NfL levels, as well as progranulin levels if appropriate. A positive family history was defined by having at least one first-degree relative with history of dementia and/or neuropsychiatric disease. All subjects underwent neuroimaging with magnetic resonance imaging (MRI) and/or cerebral 18F fluorodeoxyglucose positron emission tomography examination (18F-FDG PET).

Genetic sequencing and annotation

All patients underwent next-generation sequencing, comprising targeted exome sequencing, whole-exome sequencing (WES), or whole-genome sequencing (WGS) in isolation or in combination, in addition to *C9orf72* expansion testing. Genomic DNA was extracted from peripheral blood using QIAamp® DNA Blood Maxi Kit (Qiagen, Germany). Illumina whole-genome sequencing

(WGS), whole-exome sequencing (WES) and targeted exome sequencing was performed on 20 patients, 9 patients and 31 patients, respectively. Our targeted exome panel consisting of 200 neurodegenerative disease-related genes, has been described previously.[13] FTD-related genes in the panel included: *GRN, MAPT, TBK1, TARDBP, VCP, SQSTM1*, and *CHMP2B*.

Whole-exome sequencing with a target depth of 100X was performed with NimbleGen SeqCap EZ Human Exome Enrichment Kit v3.0 (Roche) following the manufacturer's protocol and sequenced using Illumina HiSeq4000 with 150 bp paired-end reads, whereas WGS with a target depth of 30X was performed with NEBNext Ultra II DNA Library Prep Kit on the Illumina Hiseq X Ten platform with 150 bp paired-end reads. Resulting sequencing reads were aligned to the human reference genome (hg19/GRCh37) using BWA-MEM (v0.7.15[26]), and variant calling performed using the Genome Analysis Tool Kit (GATK, v3.7[27]) following the best practices.

We then annotated variants for functional impact, population allele frequency and in silico pathogenicity prediction scores using ANNOVAR (16 April 2018 release),[28] REVEL,[29] M-CAP,[30] PrimateAI,[31] MutationTaster[32] and ClinVar.[33] Variants that were rare (MAF ≤5% of all populations, African American, American Admixed/Latino, East Asian, South Asian in gnomAD)[34] and protein altering/truncating (missense, frameshift, stop-gain, splice site disrupting) were prioritised for manual curation.

Shortlisted candidate variants were further confirmed by Sanger sequencing. Methods on Sanger sequencing, *C9orf72* expansion testing with repeat-primed polymerase chain reaction (rp-PCR) have been described previously.[21] Primer sequences are available upon request. A genetic diagnosis was conferred if a variant classified as pathogenic or likely pathogenic was identified and had appropriate clinical correlation. Variants in AD-related genes including *APP, PSEN1, and PSEN2* were additionally screened for due to their reported rare association with FTD-like phenotypes.

Biomarker analysis

Out of 60 patients, 14 had CSF and 30 had plasma collected. CSF amyloid-beta (1–42), p-tau and t-tau levels were determined by INNOTEST ELISAs (Fujirebio); CSF NfL was determined using NF-Light ELISA (UmanDiagnostics), according to the manufacturer's instructions. Plasma NfL levels were measured using ultrasensitive single molecule array (Simoa) Human NfL assay and Simoa HD-1 Analyser (Quanterix, MA), according to the manufacturer's protocol. Serum progranulin levels were measured using Progranulin ELISA (Adipogen).

Statistical analysis

Statistical analyses were performed using SPSS Statistics 23 (IBM). Mean ± standard deviation (SD) was reported for normally distributed data, median (min-max) for non-normally distributed data. Individual counts and percentage were used for categorical variables. Correlations between clinical data and NfL levels were calculated using Spearman's rank order correlation. $p < 0.05$ was considered statistically significant.

Results

Patient demographics

Demographics and clinical characteristics of FTD patients are summarised in Table 1. In the subset of patients with CSF samples collected ($n = 14$), all had CSF amyloid-beta (1–42) profiles suggestive of a non-AD aetiology.

Genetic analysis

We found predicted pathogenic/likely pathogenic mutations in FTD-related genes in 26.6% (16/60) of FTD-spectrum patients (Table 2). Demographics and clinical characteristics of these 16 patients are summarised in Table S1. Amongst patients with predicted pathogenic/likely pathogenic mutations, 8 (50%) were in the nfvPPA/indeterminant PPA group, 7 (43.8%) had bvFTD, and 1 (6.3%) was a patient with a psychiatric disorder. Genetic mutations accounted for 48% (12/25) of patients with a positive family history of dementia/psychiatric illness, and 11.4% (4/35) of cases with sporadic FTD. *C9orf72* repeat expansions were the most common pathogenic cause (13.3%, 8/60), followed by *GRN* (6.7%, 4/60) variants. No other predicted pathogenic mutations were found in other FTD-related genes. Overall, a genetic diagnosis was established in over a quarter of patients that underwent genetic testing, similar to Western cohorts.[35,36] Rare variants of unknown significance (VUS) in FTD genes are reported in Table S2. A total of seven VUS in FTD genes were found in 6 bvFTD and 1 nfvPPA/indeterminant PPA patients - two variants in *MAPT*, one variant in *GRN*, two variants in *OPTN*, one variant in *SQSTM1*, and one variant in *EIF4G1* were classified as VUS.

Association between clinical variables and NfL levels

Overall across all FTD patients with Nfl measurements, plasma and CSF NfL levels did not show significant correlation with age, disease duration and global cognitive scores ($p > 0.05$). Plasma NfL however, showed significant

Table 1. Patient demographics.

	bvFTD	svPPA	nfvPPA/indeterminate PPA	FTD-ALS	Psychiatric illness
Number	38	4	16	1	1
Age (y)	59.2 (45.0–74.2)	63.1 (56.0–70.1)	59.0 (45.2–78.8)	52.7	58.0
Age at onset (y)	57.0 (30.0–72.0)	60.0 (55.0–64.0)	59.0 (44.0–77.0)	50.0	-
Disease duration (y)	3.0 (0–24.2)	3.1 (1.0–6.1)	2.0 (0–6.0)	2.7	-
Male sex, *n* (%)	17 (45%)	1 (25%)	5 (31%)	1 (100%)	1 (100%)
Population (C:M:I:F:O)	25:2:2:7:2	4:0:0:0:0	7:0:0:8:1	1:0:0:0:0	1:0:0:0:0
Family history of dementia or psychiatric diseases, *n* (%)[1]	15 (40%)	0	9 (56%)	0	1 (100%)
CDR-SOB[2]	6.0 (1.0–18.0)	5.5 (3.0–8.0)	3.0 (0–16.0)	8	–
FTLD-CDR-SOB[3]	9.0 (3.5–24.0)	8.5 (6.0–11.0)	8.5 (1.5–22.0)	12	–
MMSE score[4]	21.0 (4.0–30.0)	14.5 (4.0–29.0)	20.0 (3.0–30.0)	–	29
MoCA score[5]	15.0 (2.0–29.0)	25	17.0 (7.0–26.0)	–	25
Plasma NfL (pg/mL)[6]	25.5 (5.0–70.8)	66.7 (37.0–119.6)	31.2 (9.0–1168.4)	206.4	17.2
CSF NfL (pg/mL)[7]	1014.4 (433–3928)	1195.6	5167.7 (626–9709)	6294.9	2361.2
Mutation	MAPT Gln351Arg, GRN Cys92Ter, TREM2 Arg47Cys, OPTN Lys328GlufsTer11, C9orf72 expansion (50–70 repeats)		GRN c.462 + 1 G > C, GRN Ser301Ter, OPTN Lys328GlufsTer1, C9orf72 expansion (35–70 repeats)		C9orf72 expansion (62 repeats)

Values are presented as median (min–max) or *n* (%). MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; bvFTD, behavioural variant frontotemporal dementia; svPPA, semantic variant primary progressive aphasia; nfvPPA, non-fluent variant primary progressive aphasia; FTD-ALS, frontotemporal dementia with amyotrophic lateral sclerosis. Race: C = Chinese, M = Malay, I = Indian, F = Filipino, O = Others. MMSE and MoCA scores presented are absolute values out of a maximum score of 30. A higher score denotes better performance. "–" = no available information.

[1]First degree family member.

[2]CDR-SOB scores are available in 55 out of 60 patients.

[3]FTLD-CDR-SOB scores are available in 37 out of 60 patients.

[4]MMSE scores are available in 49 out of 60 patients.

[5]MoCA scores are available in 44 out of 60 patients.

[6]Plasma NfL levels are available in 30 out of 60 patients.

[7]CSF NfL levels are available in 14 out of 60 patients.

correlation with FTLD-CDR-SOB (rs = 0.396, p = 0.034). Within diagnostic groups, highest plasma and CSF NfL levels were seen in nfvPPA. Within mutation carriers, eight had plasma NfL and four had CSF NfL measured (Table 2). Plasma NfL was highest at 1168 pg/mL in the patient carrying 70 *C9orf72* repeats, and CSF NfL was highest at 9709.5 pg/mL in the patient carrying a splice variant in *GRN* c.462 + 1G > C (Table 2 and Table S1).

Clinical features of pathogenic and likely pathogenic variant carriers

C9orf72 repeat expansion carriers

Two sisters of Han Chinese ethnicity were both heterozygous carriers with 70 *C9orf72* repeats. The older sister was a nurse with 13 years of education and was still working when she presented with 2-year history of predominant expressive language difficulties that started at the age of 48, followed by episodic memory impairment. Of note, she had already shown decline in judgement and behaviour that began 4 years prior to presentation, when she overused her credit card on unnecessary items ending up in debt. Upon presentation at the age of 50, she had significant difficulty with expression, but speech remained mostly fluent, and she was able to name simple items. She scored 14/30 on the MoCA test (recall 0/5 impaired retrieval on cues, impaired executive function, abstract thought, fluency (generated 2 animals) and repetition but preserved clock-drawing and naming). She had a CDR score of 2, CDR-SOB of 11.5 and FTLD-CDR-SOB score of 16.5. By the following year, she had minimal verbal output and had become wheelchair-bound and dependent for all activities of daily living (ADL). MRI brain imaging showed global cerebral atrophy advanced for age with severe frontal lobar predominance. Notably, she also carried a *GRN* Arg432Cys variant that was predicted as a VUS (see Table S2) but previously reported in association with FTD.[37] Given her PPA-type presentation, her serum progranulin levels were measured and found to be within

Table 2. Identified mutations in 16 FTD patients.

Gene	Transcript ID cDNA change	Protein change	Reference SNP (rs) ID	Phenotype	REVEL	Primate AI	M-CAP	ClinVar	Mutation Taster	gnomAD (EA)	gnomAD (AF)	NfL levels
MAPT	NM_005910.5 c.1052 A > G	Gln351Arg	rs1568339821	1 bvFTD	Pathogenic (0.83)	Tolerated (0.69)	Damaging (0.41)	Likely Pathogenic	Disease causing (0.99)	–	–	747 pg/mL (CSF), 5 pg/mL (Plasma)
GRN	NM_002087.4 c.462 + 1 G > C	–	rs794729669	1 nfvPPA[1]	–	–	–	Pathogenic	Disease causing (1.0)	–	–	9709 pg/mL (CSF), 196 pg/mL (Plasma)
GRN[18]	NM_002087.4 c.276 C > A	Cys92Ter	–	1 bvFTD	–	–	–	–	Disease causing autonomic (1.0)	–	–	–
GRN[18]	NM_002087.4 c.902 C > A	Ser301Ter	–	2 nfvPPA[1]	–	–	–	–	Disease causing autonomic (1.0)	–	–	–
TREM2[18]	NM_018965.4 c.139 C > T	Arg47Cys	rs753325601	1 bvFTD	Benign (0.43)	Tolerated (0.50)	Damaging (0.18)	-	Disease causing (0.99)	0.000109	0.000028	3928 pg/mL (CSF)
OPTN[21]	NM_021980.4 c.980 G > GA	Lys328GlufsTer11	–	1 bvFTD, 1 nfvPPA[1]	–	–	–	–	–	–	–	–
C9orf72	–	GGGGCC repeat expansion (35–70 repeats)	–	3 bvFTD, 4 nfvPPA[1], 1 psychiatric illness	–	–	–	–	–	–	–	17–1168 pg/mL (Plasma)

bvFTD, behavioural variant frontotemporal dementia; svPPA, semantic variant primary progressive aphasia; nfvPPA, non-fluent variant primary progressive aphasia; EA, East Asian; AF, allele frequency of all populations; NfL, neurofilament light chain. "–" = no available information.
[1]Cases consist of nfvPPA/indeterminate PPA.

normal limits at 132.6 ng/mL. Her younger sister presented with at the age of 44 with similar expressive difficulties and was diagnosed with nfvPPA. Neuroimaging showed prominent frontal atrophy with possibly thalamic volume loss. Both sisters did not undergo plasma/CSF NfL measurement. Their family history was notable for their late mother suffering from a history of depression and symptoms of early language impairment followed by overt dementia, passing away in her late 40 s, with maternal cousins possibly suffering from young-onset dementia (YOD).

A male carrier with 58 *C9orf72* repeats presented at age 59 with a 2-year history of progressive behavioural change and memory impairment and was diagnosed with bvFTD; brain MRI showed caudate and thalamic atrophy. He had an older brother with FTD-ALS seen in another institution who was found to be positive for a pathogenic *C9orf72* expansion[38] (testing performed overseas and reported previously). Another case was a 68-year-old man presenting with a 2-year history of progressive dysarthria, swallowing impairment and recurrent falls; family history was notable for having 3 siblings with younger-onset cognitive impairment, but no further information was available. A 66-year-old lady with bvFTD and harbouring 70 *C9orf72* repeats had a family history of ALS, but herself remained negative for anterior horn cell disease on recent electromyography testing at age 72; follow-up monitoring for clinical evolution remains ongoing. A 53-year-old lady with bvFTD presented with behavioural, language, memory, and executive function decline over 2 years. She carried 50 *C9orf72* repeats. Our oldest case carrying 35 *C9orf72* repeats is an 82-year-old lady who presented at age 76 with progressive expressive difficulties for 2 years with moderate to severe speech apraxia with component of phonemic paraphrasias. She had no family history of dementia, but both her mother and sister had expressive difficulties in their old age.

GRN mutation/variant carriers

A right-handed Indonesian-Malay male patient with 23 years of education and no other significant past medical or family history of note carried a splice variant in *GRN* c.462 + 1G > C that has been reported pathogenic in association with FTD.[39] He presented to another institution with difficulty expressing himself (but with relatively spared episodic memory) at the age of 48 that progressively worsened over 2 years gradually losing the ability to speak, read, and write. When he presented to the clinic, he was uncommunicative and unable to follow simple commands with minimal behavioural symptoms. He was diagnosed with PPA (subtype indeterminate given the advanced presentation), and his brain MRI showed

asymmetrical atrophy of the left temporal lobe. Of note, he had high CSF and plasma NfL levels of 9709.5 and 196 pg/mL, respectively (median CSF NfL in 118 healthy controls = 411 pg/mL[40]; mean plasma NfL in 50 healthy controls in our previous study = 8.8 pg/mL[41]), consistent with his relatively rapid disease progression.

The other *GRN* mutation cases in this study have been reported previously, including two novel *GRN* mutations (Ser301Ter and Cys92Ter) in three patients (one with bvFTD and two with nfvPPA) from the Philippines.[18] Most *GRN* mutations that have been described result in premature stop codons, producing mutant GRN mRNA that most likely undergoes nuclear degradation causing reduced proganulin protein levels.[42] Both Ser301Ter and Cys92Ter mutations result in premature stop codons, with 2 out of 3 patients with available plasma progranulin data demonstrating lower progranulin levels consistent with haploinsufficiency, using the proposed cutoff value of 112 ng/mL.[43]

MAPT Gln351Arg carrier

Our patient carrying the *MAPT* Gln351Arg variant that has been previously reported in FTD[44] is a 57-year-old man who presented 11 years ago at age 44 with progressive episodic memory loss and impaired judgement. There was no known family history of note. MRI brain imaging performed at presentation showed generalised cerebral and bilateral anteromedial temporal lobe atrophy advanced for age. He had a MMSE score of 29/30 and a MoCA score of 25/30 at presentation and was diagnosed with possible bvFTD then. His symptoms progressed to more profound behavioural change including stealing, repetitive actions, obsessions with bicycles, hyperorality, hoarding and loss of empathy (laughing during funerals) consistent with bvFTD. CSF NfL levels were raised at 746.8 pg/mL, while plasma NfL levels were normal at 4.98 pg/mL. Over a decade into his symptoms, his MMSE score remains at 18/30, consistent with a slow progressive disorder. He remains independent in basic activities of daily living but requires assistance for higher level instrumental ADLs.

OPTN frameshift insertion carriers

Two sisters from the Philippines who are homozygous carriers of a novel *OPTN* frameshift mutation (Lys328GlufsTer11) were previously reported by our group.[21] The proband first presented with behavioural changes at the age of 45, including decline in executive functioning, inappropriate behaviour, and social disengagement. Her scores on the MMSE and MoCA were 13/30 and 4/30, respectively. Brain MRI showed mild atrophy of both temporal lobes. She was diagnosed with bvFTD and passed away 2 years later at age 47. The proband's sister presented with word-finding difficulty and frequent pauses in her speech at 52-years-old and was non-verbal and communicating by gestures by age 55. On examination, there was decreased arm swing on the right; deep tendon reflexes were exaggerated in the right upper and lower extremities but there were no fasciculations, myoclonus or dystonia. There was positive snout reflex and positive Babinski sign bilaterally. Her MoCA score was 23/30. Brain MRI scan showed bilateral temporal lobe atrophy. FDG-PET showed mild diffuse FDG hypometabolism in the left parietotemporal cortex. EMG and muscle ultrasound showed no fasciculations. She was diagnosed with nfvPPA with a corticobasal syndrome phenotype.

TREM2 Arg47Cys carrier

The carrier is a previously reported 63-year-old right-handed female of South Asian ancestry who presented with a 5-year history of memory, language, and executive function impairment.[18] She had no significant past medical history of note and no known bone problems. Her mother was diagnosed with possible AD in her mid-70 s but no other relatives had similar symptoms. A year before presentation, she developed apathy, disinhibition, and mild ritualistic behaviour fulfilling bvFTD criteria. At presentation, she scored 10/30 on the MMSE, 2/30 on the MoCA test, 3/30 on the Boston Naming Test (BNT), and 3/12 on a test of affect naming. MRI brain revealed relatively symmetrical frontotemporal atrophy with additional biparietal atrophy, and her CSF profile was inconsistent with that of AD (CSF amyloid-beta 42: 661 pg/mL [<487 pg/mL], phosphorylated tau: 41 pg/mL [>61 pg/mL], total tau: 462 pg/mL [>425 pg/mL], with numbers in brackets denoting cut-off values suggestive of an AD-related degenerative process).

Discussion

Studies on the clinical and genetic characterisation of FTD amongst Southeast Asian countries are rare. As compared to Western cohorts, fewer Asian FTD patients have a known genetic cause.[15,16] The lower prevalence of genetic causes of FTD in some Asian cohorts has been attributed to possible underreporting of FTD due to a lack of awareness and misdiagnosis of its symptoms for psychiatric disorders, as well as limited access to healthcare and genetic sequencing in some areas.[45] To our knowledge, this is the largest genetic FTD study of well-characterised Southeast Asian patients thus far. In this study, *C9orf72* repeat expansions were the most common

genetic cause (13.3%), followed by *GRN* (6.7%) variants. Two members of the same Filipino family carried an *OPTN* frameshift insertion, while there was one carrier each of a *MAPT* and *TREM2* variant. No predicted pathogenic mutations in other FTD-related genes were found. And 48% of our patients with a positive family history of dementia and/or psychiatric illness and 11.4% of sporadic FTD patients carried a predicted pathogenic variant in an FTD-related gene. Overall, a genetic diagnosis was established in over a quarter of FTD spectrum cases that underwent genetic testing (26%), similar to Western cohorts.[35,36]

Amongst patients carrying predicted pathogenic/likely pathogenic mutations in our study, half of them (8/16) were from the nfvPPA/indeterminant PPA group, 7 (43.8%) had bvFTD, and 1 (6.3%) patient was diagnosed with a psychiatric disorder. These results were surprising given the fact that compared with the other two language variants, bvFTD has a more frequent genetic association compared to only 12% of patients with PPA[46] in some cohorts. PPA cases (comprising svPPA, nfvPPA and indeterminate PPA cases) presenting with predominant language impairment appear to occur at a higher frequency in our Southeast Asian cohort (20/60 of cases, 33%). Possible reasons for this apparent higher frequency include the fact that both institutions in this study are tertiary neurological centres with specialist YOD clinics, receiving more atypical YOD patients that present with language impairment. Unfortunately, their advanced state at presentation and the nature of local language vernacular makes classification according to standard Western-based PPA subtype diagnostic criteria difficult; as such we have classified some patients an "indeterminate".

The frequency of mutations in Chinese bvFTD patients has been reported to be close to 30% in a well-characterised cohort, and more likely to be detected in patients with a definite family history of bvFTD (87.5%).[47] PPA on the other hand, is mainly considered a sporadic disease and few studies have analysed its genetic basis, but pathogenic *GRN* variants remain the most common genetic cause found in PPA, followed by *C9orf72* expansions.[46]

C9orf72 expansions have been reported to be infrequent amongst Asian cohorts; out of 128 patients screened in mainland China, the mutation was found in only one sporadic FTD patient and a family of three with FTD-ALS (3%).[48] In our study, *C9orf72* repeat expansions were the most common genetic cause (13.3%); one patient with FTD-ALS was negative, however, for a pathogenic *C9orf72* expansion. A Taiwanese study identified large repeat expansions in three FTD patients of the same family, but not in 153 other FTD-parkinsonian syndrome patients.[49] Cohort studies of FTD patients in South Korea and Hong Kong were similarly negative for *C9orf72* expansions.[15,50,51] Other studies in Chinese FTD cohorts have also reported a comparatively low prevalence of pathogenic FTD variants ranging from 5% to 7%.[52–54] We found, however, that 50% of our positive *C9orf72* patients (8/16) carried a PPA diagnosis (language impairment being the predominant presenting symptom), while the other half were behavioural (bvFTD/psychiatric) phenotypes. None of them had significant parkinsonian features as reported in other Chinese cohorts.[47]

Similarly, whilst cases have been reported, *MAPT*[52,53] and *GRN* mutations remain less prevalent amongst Asian compared to Western cohorts.[50,55,56] A South Korean study found 2 novel missense variants of unknown significance in both *MAPT* and *GRN* in 2% of patients but did not identify any pathogenic variants.[15] In our cohort, four pathogenic/likely pathogenic mutations in *GRN* were observed in 3 nfvPPA/indeterminant PPA and 1 bvFTD; one VUS in nfvPPA/indeterminant PPA. Notably, patients carrying the four pathogenic/likely pathogenic mutations were non-Chinese (as opposed to the 9 patients carrying *C9orf72* and *MAPT* mutations are Chinese). This observation was in accordance with previous studies in China that reported less common *GRN* mutations compared to *C9orf72* and *MAPT* mutations.[53,54,57] Given the variability in genotype–phenotype correlation reported in *GRN* carriers,[58] with carriers presenting with amnestic/AD phenotypes as well, there remains the possibility that potential carriers have not been screened for or referred to our specialist clinic for genetic testing. We are unable to comment on the low prevalence in other countries/cohorts given the limited information available in the literature on this.

In this study we identified one likely pathogenic mutation and two VUS in *MAPT* in 3 bvFTD patients. The frequency of *MAPT* mutations in our cohort was low (1.7%, 1/60) compared to other Chinese FTD studies which have reported a frequency of *MAPT* variants in up to 20% of familial bvFTD[47] with *MAPT* being overall the most common pathogenic FTD gene in China at a frequency of 2.8%.[59] Possible reasons include the comparatively lower number of bvFTD patients in our cohort, many of whom are under the care of psychiatrists. Notably, our patient carrying the *MAPT* Gln351Arg variant has a slow progressive amnestic phenotype similar to another patient with a *MAPT* Gln351Arg variant with a remarkably long amnestic presentation mimicking familial AD,[44] and also displays anterior medial temporal lobe involvement consistent with known imaging signatures of *MAPT* mutations.[60–62] No pathogenic *MAPT* mutations has been found in our younger-onset AD patients.

In our cohort, mutation carriers showed no significant difference in age at onset (AAO) (mutation carriers AAO:

mean 56.5 (SD 9.9) years versus non-mutation carriers AAO: mean 57.5 (SD 7.7) years). AAO was also similar between familial (mean 57.8 (SD 8.7) years) and sporadic patients (mean 56.9 (SD 7.9) years). Within mutation carriers, those carrying *MAPT* and *OPTN* mutations had an earlier AAO: *MAPT* at 45 years, *OPTN* at mean 48.5 (SD 4.9) years; this was in accordance with previous reports of *MAPT* mutation carriers having earlier AAO.[36,63]

Both blood and CSF NfL levels have been shown to correlate with disease severity, brain atrophy, annualised brain atrophy rate and survival in genetic FTD.[19,64] We were able to measure plasma and CSF NfL levels in a subset of patients – the small sample size limited meaningful analysis but overall, plasma and CSF levels did not show significant correlation with clinical variables including disease duration and global cognitive scores. Plasma NfL however, showed significant correlation with FTLD-CDR-SOB. Within diagnostic groups, highest plasma and CSF NfL levels were seen in nfvPPA, which has been reported previously.[65] Within mutation carriers, plasma NfL was highest in the patient carrying 70 *C9orf72* repeats, and CSF NfL was highest in the patient carrying a splice variant in *GRN* c.462 + 1G > C (Table 2 and Table S1). High CSF NfL levels were previously reported to be related to *GRN*-associated FTD.[19,36,64] The potential for plasma NfL to predict disease progression in FTD with gene-specific trajectories has been reported.[66] Two distinct trajectories of plasma NfL were observed: *GRN* carriers had lower levels during the presymptomatic phase and displayed major and sustained increases after clinical onset; whilst *C9orf72* carriers displayed higher NfL levels in the presymptomatic phase, and lower levels in the clinical phase. We acknowledge that our NfL data are cross sectional, but this provides a preliminary understanding of NfL levels in Asian genetic FTD and highlights the importance of NfL data in genetic FTD across various cohorts and ethnicities. The gene-specific reference levels across various cohorts may also be useful for clinical and therapeutic trials in genetic FTD/ALS.

Limitations of our study include the lack of pathological diagnosis, limited clinical information from their treating physician in some patients, limited CSF and blood draw, as well as lack of detailed information about family history. Given that these cases were seen in a tertiary specialist neurocognitive clinic with an interest in neurogenetics, we acknowledge the potential selection bias in some of these cases. However, this remains the first and largest comprehensive study characterising the spectrum and phenotypes of genetic FTD cases in Southeast Asia, incorporating biomarker measurements in a subset of patients.

Our findings show that genetic mutations accounted for over one-quarter of our FTD-spectrum cases in our cohort, including those with sporadic or unknown family history. This highlights the importance of wider implementation of genetic testing in FTD patients from Southeast Asia. Future directions include expanding our FTD genetic studies to include more collaborators across other Southeast Asian countries to allow further study on genotype–phenotype correlations, inheritance and/or penetrance patterns that may be unique to cases in this part of the world.

Author Contributions

ASLN and YJT designed the study. YJT, ACWY, JD, ZHF, KN, HJC, KPN, SKST, NK and ASLN acquired the data relevant for the study. YJT, JNF, MML, WKL, ALSN analysed, interpreted the data, and drafted the manuscript. All authors contributed to the writing and revisions of the paper and approved the final version.

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Conflicts of Interest

The authors declare that they have no competing interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Tables S1 and S2.

