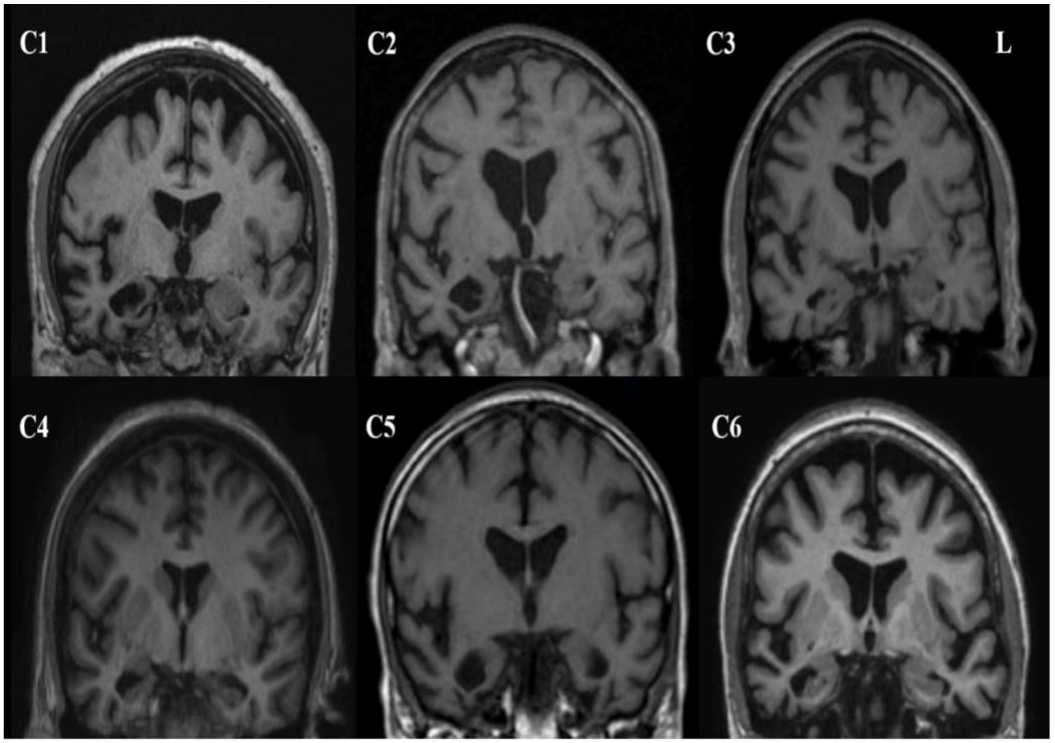
Supplementary Material

The Right Temporal Variant of Frontotemporal Dementia Is Not Genetically Sporadic: A Case Series

Supplementary Figure 1. Coronal sections of structural T1 weighted MRI scans of the patients. Right predominant temporal lobe atrophy. C1, C2, C4, C5, and C6 show prominent right predominant temporal atrophy whereas C3 shows only marginal right sided temporal atrophy.



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Supplementary Material 1

Genetic Assessment

Amsterdam Dementia Cohort

Genomic DNA was extracted from peripheral-blood leukocytes according to standard procedures.

WES was performed. DNA was enriched using the SeqCap capturing kit for Illumina Paired-End Sequencing library (version 2.0.1; NimbleGen). The captured fragments were purified and sequenced on an Illumina Hiseq4000 platform using 100 bp paired-end reads. The average coverage of the exome is ~50x with a minimum depth of >30 reads. Duplicate reads were excluded. Data were demultiplexed with bcl2fastq Conversion Software from Illumina. All sequence reads were mapped to GRCh37/hg19 reference genome using Burrows-Wheeler Aligner (BWA) Tool. GATK was used for variant calling and quality control according to best practice [1]. Population database frequencies (gnomAD v2.1.1), functional and impact-score annotations were assigned to variants using ANNOVAR [2]. The WES data was analyzed with Alissa Interpret software from Agilent. Additionally, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis was performed for *APP* (SALSA P170 APP; MRC Holland) and *PSEN1* (SALSA P254 PSEN1; MRC Holland). For *C9orf72*, a repeat expansion test was performed (commercial kit Asuragen® AmplideX PCR/CE).

Istanbul University Dementia Cohort

Genomic DNA was isolated from the collection of 2 ml venous blood in K3EDTA tubes by kit (MagNA Pure Compact Nucleic Acid Isolation Kit-Large Volume; Roche). Primers were designed to cover all coding exons and exon-intron boundaries of *MAPT* (NM_005910.5), *GRN* (NM_000512.4). Sequencing primers are available from the authors upon request. Sanger sequencing reaction was performed on capillary electrophoresis (ABI

3130) and analyzed using SeqScape software version 2.7 (Applied Biosystems, Bedford, MA, USA).

Pathological Assessment: Amsterdam Dementia Cohort

Pathological assessment was available for only one case (Case 3). Comprehensive neuropathological assessments were performed following previously described standard procedures for the evaluation of frontotemporal dementia [3]. The neuropathological diagnosis of FTLD [4] and FTLD-*MAPT* [5] was made using standard criteria.

List of genes causing or associated with FTD, FTD-ALS, or other early-onset dementias, investigated by whole exome sequencing or targeted high-throughput panel sequencing (Alzheimer Dementia Cohort)

ALS2: Amyotrophic lateral sclerosis 2
ANG: Angiogenin
APOE: Apolipoprotein E
APP: Amyloid Beta Precursor Protein
ATP7B: ATPase activity, 7 distinct domain, and B class for second P-type ATPase copper binding pump
C19orf12: Chromosome 19 Open Reading Frame 12
C9orf72: Chromosome 9 open reading frame 72
CCNF: Cyclin F
CHCHD10: Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10
CHMP2B: Chromatin-modifying protein 2B
CLN3: Ceroid Lipofuscinosis Neuronal Protein 3
CLN5: Ceroid Lipofuscinosis Neuronal Protein 5
CSF1R: Colony Stimulating Factor 1 Receptor
CTSD: Cathepsin D
EIF4G1: Eukaryotic Translation Initiation Factor 4 Gamma 1
ERBB4: Tyrosine-protein kinase erbB-4
GRN: Progranulin
FUS: Fused in sarcoma
HNRNPA1: Heterogeneous nuclear ribonucleoprotein A1
HNRNPA2B1: Heterogeneous Nuclear Ribonucleoprotein A2/B1
HTRA1: HTRA serine peptidase 1
ITM2B: Integral membrane protein 2B
MAPT: Microtubule associated protein tau
NOTCH3: Notch homolog 3
NPC1: Intracellular cholesterol transporter 1
NPC2: Intracellular cholesterol transporter 2
OPTN: Optineurin
PDGFB: Platelet derived growth factor subunit B
PPT1: Palmitoyl-protein thioesterase 1
PSEN1: Presenilin 1
PSEN2: Presenilin 2
SOD1: Superoxide dismutase 1
SQSTM1: Sequestosome
TARDBP: TAR DNA binding protein
TIA1: T-cell-restricted intracellular antigen-1
TBK1: TANK binding kinase 1
TREM2: Triggering Receptor Expressed On Myeloid Cells 2
UBQLN2: Ubiquilin 2
VCP: Valosin-containing protein
VPS13A: Vacuolar protein sorting-associated protein 13A
XPR1: Xenotropic And Polytropic Retrovirus Receptor 1

List of genes causing or associated with FTD, FTD-ALS, or other early-onset dementias, investigated by whole exome sequencing or targeted high-throughput panel sequencing (Istanbul University Dementia Cohort)

APOE: Apolipoprotein E
APP: Amyloid Beta Precursor Protein
C9orf72: Chromosome 9 open reading frame 72
CHCHD10: Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10
DCTN1: Dynactin Subunit 1
GRN: Progranulin
MAPT: Microtubule associated protein tau
PSEN1: Presenilin 1
PSEN2: Presenilin 2
SNCA: Synuclein Alpha
SNCB: Synuclein Beta
SOD1: Superoxide dismutase 1
TREM2: Triggering Receptor Expressed On Myeloid Cells 2
UBQLN2: Ubiquilin 2
TUBA4A: Tubulin Alpha 4a
VPS13A: Vacuolar protein sorting-associated protein 13A

Supplementary Material 2

Case 1

A 59-year-old, right-handed male presented with a 2-year history of progressive personality change including sadness, losing initiative and aggressiveness. He was unaware of his mental symptoms. Moreover, he had developed memory problems and started getting lost in routine surroundings. He also started to drink alcohol excessively.

The neurological examination was normal and the neuropsychological examination showed deficits in memory and learning ability at the initial visit. Levels of CSF amyloid-beta 42, total tau and phospho-tau were within normal limits (Tijms *et al.*, 2018) (Table 1). The MRI revealed asymmetric cortical atrophy of the temporal lobes including strongly asymmetric right over left MTA (Scheltens *et al.*, 1992) (Table 1). No vascular abnormalities were detected (Fig. 1). Genetic testing showed a heterozygous pathogenic variant in the *GRN* gene (NM 002087.3) c.388_391del, p.(Gln130Serfs*125).

Case 2

A 64-year-old, right-handed female presented with an 8-year history of behavioral changes and memory deficit. Since the death of her husband eight years before, she had suffered from a headache that grew worse over the years and it made her dominantly sad. She sold their own restaurant one year after the death of her husband because she could not manage it. She gradually showed less initiative and became more depressive. Subsequently, her self-care concerning clothing diminished. After a few years, memory problems emerged, while she started to exhibit compulsive eating, disinhibition, and changes in social conduct. The patient presented also compulsive symptoms such as living with a fixed time schedule and walking several miles every day. She had difficulty recognizing family members with some additional problems recognizing objects.

Her brother and aunt were diagnosed with FTD and 4 sisters were diagnosed with presenile dementia (Table 1).

At the initial visit the neurological examination was normal, except for remarkable aprosodia. The neuropsychological examination revealed mild deficits in cognitive functions. She had a high distractibility and less overview. CSF amyloid-beta 42, total tau, and phospho-tau were normal (Table 1). Her MRI showed asymmetric atrophy of the temporal lobes in both cortical and mesial temporal areas (Table 1, Fig. 1). Additionally, partly confluent white matter hyperintensities were reported on T2 and FLAIR scans. Genetic testing showed a heterozygous predicted likely pathogenic variant in the *MAPT* gene (NM 005910.5) c.914G>C, p.(Ser305Thr).

Upon clinical follow up her symptoms gradually declined. She got lost in her neighborhood with orientation problems. She did not know how to set the table and ate quickly without manners. She had stereotypical speech, echolalia and apraxia. Her cognitive problems worsened in 10 years after the initial symptoms and she was taken to a nursing home.

Case 3

A 58-year-old, right-handed male, presented with a 4-year history of depression, panic, aggression, social withdrawal, and progressive memory problems. At the initial visit, loss of initiative and excessive daytime sleepiness were prominent as well. Over the next year, he became obsessed with schedules. Moreover, he played golf every day and he was obsessive to become the best golf player in the Netherlands. Over the consecutive months, his cognitive decline progressed. He had periods with excessive money spending. His self-care declined, and he lived for 12 days without showering. He became more childish, disinhibited, egocentric, and he was not aware of his symptoms. He was suffering from various physical pains that was interpreted as hypochondria and he developed prosopagnosia.

The family history showed no dementia, but his mother attempted suicide.

His neurological examination was normal, whereas the neuropsychological tests showed episodic memory problems at the initial visit (Table 1). The MRI showed marginal atrophy in the parietal and frontal areas as well as in the temporal lobes. Even though the initial MRI showed marginal atrophy on the right side (Table 1, Fig. 1), the ^{18}F-FDG PET showed isolated hypo-metabolism in the right temporal lobe. Genetic analysis revealed a heterozygous variant of unknown significance in the *MAPT* gene (NM 005910.5) c.1055C> T, p.(*Ser352Leu*). This variant has previously only been described in homozygous state in two

siblings with FTD. Because no second (pathogenic) variant was found in the *MAPT* gene, the clinical significance of this (heterozygous) variant in our patient is unclear.

Three years after his initial symptoms he was completely dependent in daily living activities, had less spontaneous speech and he progressed with a neuroleptic related tremor and tardive dyskinesia. He died 8 years after the initial visit. Postmortem pathological examination revealed distinct asymmetric right-sided frontotemporal atrophy and extensive 3RD and 4RD tauopathy, also in glial cells. There were no Pick bodies. The pathological features were suggestive for a pathogenic variant in the *MAPT* gene (Fig. 2).

Case 4

A 53- year-old, right-handed, female, presented with a 1-year history of episodic memory deficit. Mainly, she had problems with remembering names and events. She was working as a speech therapist and she did not concern herself as a patient. According to her colleagues and her husband, she became more depressive and less initiative. At the first year follow up, her short-term memory was reduced, and she became stubborn to go outside and cycle faster and faster every day. Her colleagues complained about her behavioral changes. Due to conflict of labor, she became unemployed which made her more depressive. Over the consecutive months, her memory deficit progressed, and naming problems occurred. At the following visit, she was less emphatic, insecure, and fixed in time and schedule.

Her family history was positive for dementia. Her mother and 4 brothers were diagnosed with dementia between the age of 50 and 60. Additionally, her cousin and niece were diagnosed with dementia at early ages.

Except left sided torticollis, her neurological examination was normal. Cognitive tests revealed a moderate learning and memory deficit at the initial visit. CSF amyloid-beta 42, total tau, and phospho-tau were normal (Table 1). MRI showed bilateral temporal atrophy;

right greater than left (Fig. 1, Table 1). Genetic analysis revealed a pathogenic variant in the *MAPT* gene, (NM 005910.5) c.1216C> T, p.(*Arg406Trp*).

Her follow-up continues and currently, she is relatively independent in her daily activities.

Case 5

A 63-year-old, right-handed male was referred to our clinic due to a 1-year history of behavioral changes. These consisted of mainly socially inappropriate behavior. He had become rude and argumentative in the family and social settings. He was neglectful toward the feelings of his family members and showed no accustomed restraint in dealing with unfamiliar people. He had become gluttonous, indulging in sweet fads, and consuming an excessive amount of jam. One year after his initial symptoms, he developed prosopagnosia and experienced language problems, such as single-word comprehension deficit and object naming.

His family history was positive for dementia. He was the third of the five children of non-consanguineous parents. His father was demented when he died in his early 60s. No further information was available about the dementia profile. A nephew was reported to suffer from an early onset behavioral and memory impairment, and one niece died at the age of 57 after the clinical onset of similar symptoms at the age of 50.

Neurologic examination revealed subtle motor signs, such as Myerson's sign, mild axial rigidity, and reduced left-arm swing. His MMSE score was 29/30. His initial mental status examination showed problems in complex attention, as evidenced by reduced digit span, impaired serial recitations, and increased Stroop interference time, and he gave concrete interpretations to several common proverbs. His linguistic skills were intact, including single-word comprehension and visuoperceptual skills were also intact, including famous face

recognition. Otherwise, he had no problems with memory, language, and navigational skills, and his usual activities of daily living (ADLs) were mostly intact.

The MRI showed marked anterior temporal atrophy; right greater than left (Fig. 1). Genetic analysis revealed a pathogenic variant in the *MAPT* gene (NM 005910.5) c.902C>T p.(*Pro301Leu*).

The patient had a 4-year follow-up in our clinic up until shortly before his death. Over the years, as the behavioral problems worsened, familiar face recognition and single-word comprehension problems appeared in parallel. Once, his wife was astonished to hear the patient asking what a “ball” could mean. These problems were reflected in the patients' declining performance in tests of confrontation naming, verbal fluency, semantic memory, and familiar face recognition. During the second part of his follow-up, his navigational skills started to be impaired, and he was lost several times in the environment as he attempted to wander around in inappropriate times and with inappropriate attire. He was incontinent, and behavioral disinhibition stood as the major problem disrupting the ADLs towards the end. Initial motor signs did not evolve any further.

Case 6

A 58-year-old, right-handed, female presented with behavioral problems and memory deficit. According to patient’s husband, the problems started 11 years ago. She had withdrawn socially and had increasingly focused on physical complaints. There had been several therapies and diagnoses like fibromyalgia, but no one really could help her, and no real diagnosis had been made in spite of her excessive medical help seeking. Ten years after her initial problems, she became more egocentric and she started to repeat the same routine, for instance cooking the same food three times a week and obsessed with baking. She was still suffering from severe pain and she had to lie down, even this happens in the middle of the

street. Preoccupation with her body and health was continuing and she had several treatments such as supplements and ozone therapy. She was no longer able to remember the recent events easily and had problems to manage and organize her life. Over the consecutive months, she became addicted with jigsaw puzzles and had difficulties sleeping and sitting due to motor restless.

Family history was not strong for dementia. Her grandfather was diagnosed with dementia at the age of 72; however, the type of dementia is unknown. Her brother was diagnosed with autism spectrum disorder and had drugs and alcohol abuse.

The neurological examination was normal. Cognitive tests revealed a moderate memory deficit. CSF amyloid-beta 42, total tau, and phospho-tau were normal (Table 1). MRI showed bilateral temporal atrophy; right greater than left (Fig. 1, Table 1). Genetic analysis revealed a heterozygous variant of unknown significance in the *TARDBP* gene, (NM007375.3) c.1147A>G, p.(*Ile383Val*).

She has been diagnosed with FTD recently and she is still under our follow-up. Currently, she is relatively independent in her daily activities.

REFERENCES

[1] McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, Garimella K, Altshuler D, Gabriel S, Daly M, DePristo MA (2010) The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res* **20**, 1297-1303.

[2] Wang K, Li M, Hakonarson H (2010) ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* **38**, e164.

[3] Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJM, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DMA (2009) Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol* **119**, 1-4.

[4] Mackenzie IRA, Neumann M (2016) Molecular neuropathology of frontotemporal dementia: insights into disease mechanisms from postmortem studies. *J Neurochem* **138**, 54-70.

[5] Kovacs GG (2015) Invited review: Neuropathology of tauopathies: principles and practice. *Neuropathol Appl Neurobiol* **41**, 3-23.

[6] Tijms BM, Willemse EAJ, Zwan MD, Mulder SD, Visser PJ, van Berckel BNM, van der Flier WM, Scheltens P, Teunissen CE (2018) Unbiased approach to counteract upward drift in cerebrospinal fluid amyloid-β 1–42 analysis results. *Clin Chem* **64**, 576-585

[7] Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, Kuiper M, Steinling M, Wolters EC, Valk J (1992) Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* **55**, 967-972.