Phenotypic variability in early-onset dementia segregating with a novel *APP* (p.I718M) variant

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Family summary

The family was of Assyrian-Iraqi origin and native tongue was Arabic/Assyrian, but the siblings in the study (III:1-5) had emigrated to Sweden in their teens or 20s (living in Sweden >25 years) and spoke Swedish fluently. Four siblings had a history of depression or anxiety syndrome, one of diabetes mellitus type 2, two with hypertension, one with dyslipidemia, one with prior thyreotoxicosis, one with asthma, and one had undergone surgery of a malignant lung tumour. III:4 had a previously known traumatic brain lesion in the frontal cortex as described below, albeit without any known neurological sequelae. There were no cases of ischemic cardiac disease, peripheral vascular atherosclerosis or cerebral ischemic events such as stroke or transient ischemic attack (TIA), nor of neurological disease other than secondary epilepsy. All were non-smokers and had none or very limited alcohol intake. In all, the siblings were relatively healthy and lacked current significant somatic health issues affecting daily life. A description of the clinical course is presented in three siblings (III:1, III:2 and III:4), for whom we had specific consents for presenting detailed case reports.

Sibling III:1

The proband (III:1) was previously healthy and had an insidious symptom onset, including memory impairment, at 47 years of age. Initial memory investigation at 49 years of age indicated a personality change, impairment of executive function, visuospatial abilities, subtle impairment of speech and frontal behaviour. III:1 was reported to have difficulties orienting herself at work. III:1 had a normal neurological examination, MMSE score 18/30 and was

APOE ε4/ε4 homozygous. Assessment of the Clinical Dementia Rating (CDR) scale provided global CDR 2 and CDR sum of boxes 10. EEG findings included unspecific mild to moderate episodic slowing of the posterior dominant EEG rhythm, possibly related to fluctuating vigilance level. No epileptic discharges were observed. A decrease in blood flow was observed in parietotemporal cortex using SPECT, as well as a bilateral decrease in the superior parietal cortex. MRI did not detect any global cortical atrophy (GCA 0) or atrophy in medial temporal lobes (MTA 0), and only solitary white matter lesions located parietally and adjacent to the lateral ventricles' occipital horns bilaterally (Fazekas 1). [18F]-Flourodeoxyglucose (FDG)-PET showed a pronounced decrease of metabolism in parietal cortex congruent to other imaging and, in addition, a decreased metabolism in regions of frontal cortex. Re-analyses of frozen stored CSF-samples indicated decreases in concentration of CSF Aβ42 (43pg/mL, reference >550pg/mL) and Aβ42/40 ratio (0.18, reference >0.89) and increases in p-tau181 (99.1pg/mL, reference <50pg/mL), t-tau (562pg/mL, reference <409pg/mL) and NfL (778pg/mL, reference <632pg/mL). III:1 was clinically diagnosed with EOAD at the age of 50 and started treatment with Reminyl. Reassessment of the diagnosis as part of the study confirmed that III:1 fulfilled criteria of probable AD with evidence of an AD pathophysiological process (biomarker support of amyloid and tau pathology) (McKhann et al., 2011). III:1 was admitted and started neuroleptic treatment (Risperidon) for treatment of severe paranoid delusions and agitation shortly after being diagnosed, sometimes not recognizing next-of-kin. The disease rapidly progressed, with severe behavioral and psychological symptoms of dementia (BPSD), apraxia and deterioration of memory, language and visuospatial abilities. Memantine was discontinued after a short period due to worsening of BPSD, while neuroleptic treatment continued. III:1 moved to a memory care facility at the age of 52 and died at the age of 59, after a duration of 12 years from symptom onset. Neuropathological examination determined a diagnosis of definitive Alzheimer disease according to CERAD criteria, Braak stages V-VI and an A3B3C3 score according to NIA-AA criteria. Cerebral amyloid angiopathy (CAA) type-2 was reported as moderate to severe and LB pathology was consistent with amygdala-predominant LBD (Fig. 3).

Sibling III:2

III:2 had a medical history of hypertension, insomnia and prior thyrotoxicosis. Next-of-kin reported symptom onset with impaired memory at 59 years of age, two years before baseline

cognitive investigation and in parallel to diagnosis of thyreotoxicosis and symptoms of depression and anxiety. Although memory impairment was the first detected symptom, similar to that observed in the other siblings, visual and hearing hallucinations and increased passivity were exacerbated before and around cognitive investigation. Antipsychotic treatment was initiated the year before memory investigation, but was discontinued a few weeks before initial memory investigation due to suspected parkinsonian side effects. Next-of-kin reported unchanged symptoms before and after discontinuation of antipsychotic treatment. At the initial memory investigation, the MMSE score was 16/30 and neurological symptoms of parkinsonism were noted, including left-sided cogwheel rigidity and bradykinesia, impaired strength in the left lower extremity, anterior leaning posture, staring gaze, possible central facial palsy (corner of mouth), hypophonia and a symmetric hyperexcitability of peripheral reflexes. Also, there was a history of hyposmia (before COVID-19). Assessment of motor symptoms using MDS-UPDRS part III rendered a score of 12 points, corresponding to mild parkinsonism. Blood pressure test did not indicate any significant orthostatic hypotension. A follow-up assessment at the Neurology clinic also described mild left-sided bradykinesia, mild rigidity in the right upper extremity, clonus in patellar reflexes (1-3) and impaired saccades in vertical eye movements, including a decrease in amplitude. The patient could easily rise from a chair, had no tremor and had a normal retropulsion test. Cognitive testing was performed by an occupational therapist at the Clinic for Cognitive Disorders at Karolinska University Hospital and indicated a major deterioration of memory, executive function and visuospatial deficits. There was a fluctuation of cognition and alertness. Nocturnal hallucinations and vivid dreams, but no information on aberrant motor behavior during sleep, were reported. *APOE* status detection indicated ε3/ε4 heterozygosity. MRI showed no medial temporal lobe atrophy (MTA 0-1), global atrophy (GCA 0) or white matter changes (Fazekas 0). EEG detected occurrence of diffuse bilateral theta activity (4-7Hz), but within normal range. I-123-Dopamin-ioflupane (DaTscan) scintigraphy showed a pronounced decrease in isotope uptake in the putamen and nuclei caudate bilaterally (right-side dominant), suggesting nigrostriatal dopaminergic degeneration. The patient received Mirtazapin and SSRI during DatScan, but not neuroleptic treatment. Re-analyses of frozen stored CSF-samples showed decreased concentrations of CSF Aβ42 (431pg/mL, reference >550pg/mL) and Aβ42/40 ratio (0.84, reference >0.89) and an increase of p-tau181 (59.4pg/mL, reference <50pg/mL). Concentrations of t-tau (332pg/mL, reference <409pg/mL) and NfL (580pg/mL, reference <632pg/mL) were within normal intervals. III:2 was clinically diagnosed with DLB at the age of 61 years and started treatment with ChEI and levodopa. Retrospective calculation

of CDR determined a global CDR score of 1 and CDR sum of boxes of 9 points at diagnosis. Reassessment of the diagnosis and fluid biomarkers was performed as part of this study. First, due to evidence of mixed aetiology (symptoms of Lewy body disease) III:2 was categorised as having possible AD with evidence of an AD pathophysiological process (biomarker support of amyloid and tau pathology) according to NIA-AA guidelines (McKhann et al., 2011). In parallel, three core DLB criteria (fluctuating cognition and alertness, visual hallucinations and parkinsonism) and one indicative criterion (reduced dopamine transporter uptake in basal ganglia) were fulfilled, sufficient for a diagnosis of probable DLB (McKeith et al., 2017). Supportive clinical features included hyposmia, hallucinations of other modalities, delusions and other psychiatric symptoms (apathy, anxiety and depression). Also, supportive biomarkers included the relative preservation of the medial temporal lobe (MRI). However, REM sleep behaviour disorder and autonomic dysfunction (including orthostatic hypotension) were not observed, and EEG findings were within normal range. Biomarker findings of AD pathology (CSF Aβ42/40 ratio, Aβ42/38 ratio, Aβ42, p-tau181 and p-tau181/Aβ42 ratio) supported a mixed aetiology that would in part explain the clinical syndrome, rendering a diagnosis of possible DLB. Together, the diagnosis was reassessed to fulfil the criteria of mixed AD/DLB. Within a year of the diagnosis, the sibling was admitted to inpatient geriatric care due to agitation and BPSD. The diagnosis was not changed during the course of the disease, albeit a neurologist at the Memory clinic considered other diagnoses of cognitive disease due to rapid deterioration of cognitive symptoms concomitant to mild parkinsonian symptoms. The subsequent year, the patient experienced daily hallucinations and was diagnosed with a Capgras delusional syndrome. The patient later received a percutaneous endoscopic gastrostomy (PEG) for administration of enteral nutrition and, with time developed mutism, severe rigidity, spastic tetraparesis, obstipation and colonic pseudo-obstruction (Ogilvie's syndrome). Several different drugs targeting BPSD and psychotic symptoms were used during the years, including Sertraline (SSRI), Mirtazapin and Quetiapin.

Sibling III:4

III:4 had a history of mild depression, hypertension, asthma and mild diabetes mellitus type 2. A partial pulmonary surgical resection was performed due to lung cancer two years prior to the memory investigation, without any relapses. Next-of-kin reported an insidious onset of

memory impairment at the age of 67, two years before initial memory investigation. Memory investigation indicated an impairment in memory and visuospatial abilities. Neurological examination was normal and the MoCA score was 14/30. *APOE* status detection indicated ε3/ε4 heterozygosity. Retrospective calculation determined scores of global CDR 2 and CDR sum of boxes 10. MRI showed an older known traumatic residual lesion in left frontal cortex, central atrophy, subtle atrophy of the superior vermis and last, solitary microhemorrhages in the right temporal lobe. Scoring showed Fazekas 1, GCA 1, MTA 2 and 2-3 (right: left). [18F]Flutemetamol PET five years after symptom onset showed pronounced pathological uptake of [18F]Flutemetamol in most of the brain, including frontotemporoparietal areas and basal ganglia. Re-analyses of frozen stored CSF-samples indicated decreases in the concentrations of CSF Aβ42 (422pg/mL, reference >550pg/mL) and in the Aβ42/40 ratio (0.57, reference >0.89) and increases in p-tau181 (150.6pg/mL, reference <50pg/mL) and t-tau (890ng/L, reference <409pg/mL). Concentration of CSF NfL (1012pg/mL, reference <1314pg/mL for age >60 years) was within normal interval. III:4 was diagnosed with AD at the age of 69 and started treatment with ChEI. Reassessment of the diagnosis as part of the study confirmed that III:4 fulfilled criteria of probable AD with evidence of an AD pathophysiological process (biomarker support of amyloid and tau pathology) (McKhann et al., 2011). The disease later slowly progressed. Mirtazapin was initiated towards irritability and subtle delusions two years following diagnosis. III:4 was still living at home with aid from next-of-kin and home care seven years since onset of symptoms.

Neuropathological examination

Neuropathological examination was performed in the proband (III:1). The left hemisphere from the post-mortem brain was frozen in block sections, and the right hemisphere was fixed in 4% formaldehyde before being further processed. Material for microscopical examination was collected according to a protocol for neurodegenerative disorders and included all cerebral lobes, the anterior and posterior parts of the hippocampus, amygdala, basal ganglia, thalamus, mesencephalon, brainstem and cerebellum. Staining of 5 µm thick paraffin sections was performed with hematoxylin-eosin, Luxol fast blue and Bielschowsky silver stain. A few regions were also stained for amyloid with Congo staining. Immunohistochemical (IHC) staining was performed on selected regions with antibodies against Aβ1-40 and Aβ1-42 (clone G2-10 and G2-11 respectively, Merck Millipore) (basal ganglia, cerebellum, frontal

and parietal lobe), tau AT8 (Thermo Fisher scientific) (basal ganglia, hippocampus, frontal and occipital lobes), α-Synuclein (clone 5G4, Merck Millipore) (mesencephalon, amygdala, gyrus cinguli, frontal lobe, pons and medulla oblongata) and pTDP-43 (polyclonal Ser409.Ser410, Invitrogen) (amygdala, hippocampus and the frontal lobe).

The right cerebrum weighed 340 grams, the right cerebellar hemisphere 60 grams and the right part of the brainstem 10 grams. Gross inspection of the post-mortem brain showed severe atrophy of the gyri, especially prominent in the frontal lobe. In coronal sections of the brain, reduced thickness of the cortex was present, sometimes measuring only a mm. The hippocampus was atrophic, especially in the anterior part, as was the amygdala. There was a pronounced dilatation of the lateral ventricle. The brainstem and cerebellum were macroscopically normal. Microscopically, frontal and parietal cortices showed pronounced changes, including degeneration of neurons and an increased number of glial cells, while other cortices seemed somewhat better preserved. Numerous neuritic plaques and NFTs were present in Bielschowsky silver staining in all lobes, including the occipital lobe. Similar changes were found in the hippocampus, entorhinal cortex, and amygdala, as were ghost tangles. NFTs were seen in the basal nucleus and thalamus. Diffuse plaques were detected in the putamen. Some losses of pigmented neurons were observed in the substantia nigra. A slight loss of Purkinje cells was noticed in sections from the cerebellum. Congo staining was positive in the walls of vessels in the leptomeninges and cortex. Immunohistochemistry was positive for Aβ1-40 in numerous vessels in the cerebral cortex and leptomeninges, and in the leptomeninges of the cerebellum. Also, some plaques were positive for Aβ1-40. No plaques were detected in the basal ganglia. Numerous diffuse and neuritic cortical plaques, with a central core, were positive for Aβ1-42. Vessels in the leptomeninges showed varying positivity for Aβ1-42 in the walls. Many diffuse plaques were present in the putamen. In the cerebellum, diffuse staining was noticed in the molecular layer and in some leptomeningeal vessel walls. For tau, prominent immunopositivity was observed in the cortical neuropil and in the cytoplasm of neurons. A similar prominent reactivity was found in the hippocampus and the basal nucleus. Intracytoplasmatic tau positivity was also present in the granular layer of the dentate gyrus. For α-Synuclein, many neurons and threads were positive in the amygdala, while only a few positive threads were found in the cingulate gyrus and substantia nigra. No immunopositivity was detected in the cerebral cortex, pons or medulla oblongata. There was no immunoreactivity for pTDP-43.

In all, IHC and Bielschowsky silver staining confirmed advanced stage AD neuropathological change, with amyloid plaques in cerebellum (Thal phase 5), neocortical neurofibrillary tangles (NFTs) (Braak stages V-VI) and frequent amyloid neuritic plaques in cerebral cortex (definite AD according to CERAD criteria). Frequent Congo and IHC positive vessels/arteries were identified in the leptomeninges and cortex, corresponding to moderate to severe CAA type 2. Last, findings of α-Synuclein positivity corresponded to amygdala-predominant Lewy body disease (Fig. 3).

Applying NIA-AA guidelines, neuropathological findings of amyloid pathology and NFTs scored as A3, B3, C3, corresponding to a “high” AD neuropathologic change and fulfilling criteria to explain the clinical syndrome (Hyman et al., 2012). In contrast, amygdala-predominant Lewy body disease is currently not considered enough to explain the clinical syndrome (McKeith et al., 2017).

Gene panels

Gene panel, version 2 (sibling III:1): *APP*, *PSEN1*, *PSEN2*, *PGRN*, *MAPT*, *TBK1*, *TARDBP*, *VCP*, *FUS*, *SOD1*, *CHMP2B*, *SNCA*, and *LRRK2*. Additional analysis was performed for copy number variation in *APP* and *PGRN* with Multiplex Ligation-dependent Probe Amplification, (MLPA, MRC Holland, Amsterdam, Netherlands) and repeat-expansion mutations in the *C9orf72*-gene.

Gene panel, version 8 (siblings III:2, III:3, III:5): *ABCD1, AFG3L2, ALS2, ANG, ANXA11, APP, ARSA, ATP13A2, ATP1A3, ATP7B, AUH, C19orf12, CACNA1G, CCNF, CHCHD10, CHCHD2, CHMP2B, CLCN2, CLN6, COASY, COL4A1, COL4A2, CP, CSF1R, CTSA, CTSF, CYLD, CYP27A1, CYP7B1, DARS2, DCTN1, DNAJC5, DNAJC6, DNMT1, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, ELOVL4, EPM2A, ERBB4, FBX07, FIG4, FTL, FUS, GBA, GCH1, GFAP, GLA, GRN, GSN, HEXA, HEXB, HNRNPA1, HTRA1, ITM2B, JAM2, KCNC3, KCND3, KIF5A, LAMB1, LRRK2, LYST, MAPT, MATR3, NHLRC1, MYORG, NOTCH3, NPC1, NPC2, OPA3, OPTN, PANK2, PARK7, PDGFB, PDGRB, PFN1, PINK1, PLA22G6, PLD3, PRKN, PRKRA, PRNP, PRPH, PSEN1, PSEN2, RAB39B, RNF216, SETX, SIGMAR1, SLC20A2, SLC30A10, SNCA, SOD1, SORL1, SPAST, SPG11, SPR, STUB1, SQSTM1, SYNJ1, TARDBP, TBK1, TMEM240, TREM2, TREX1, TTC19, TTR, TUBA4A, TUBB4A, TYROBP, UBQLN2, VAPB, VCP, WDR45, VPS13A, VPS35, XPR1*.

Supplementary Table 1. Demographical data and plasma biomarkers

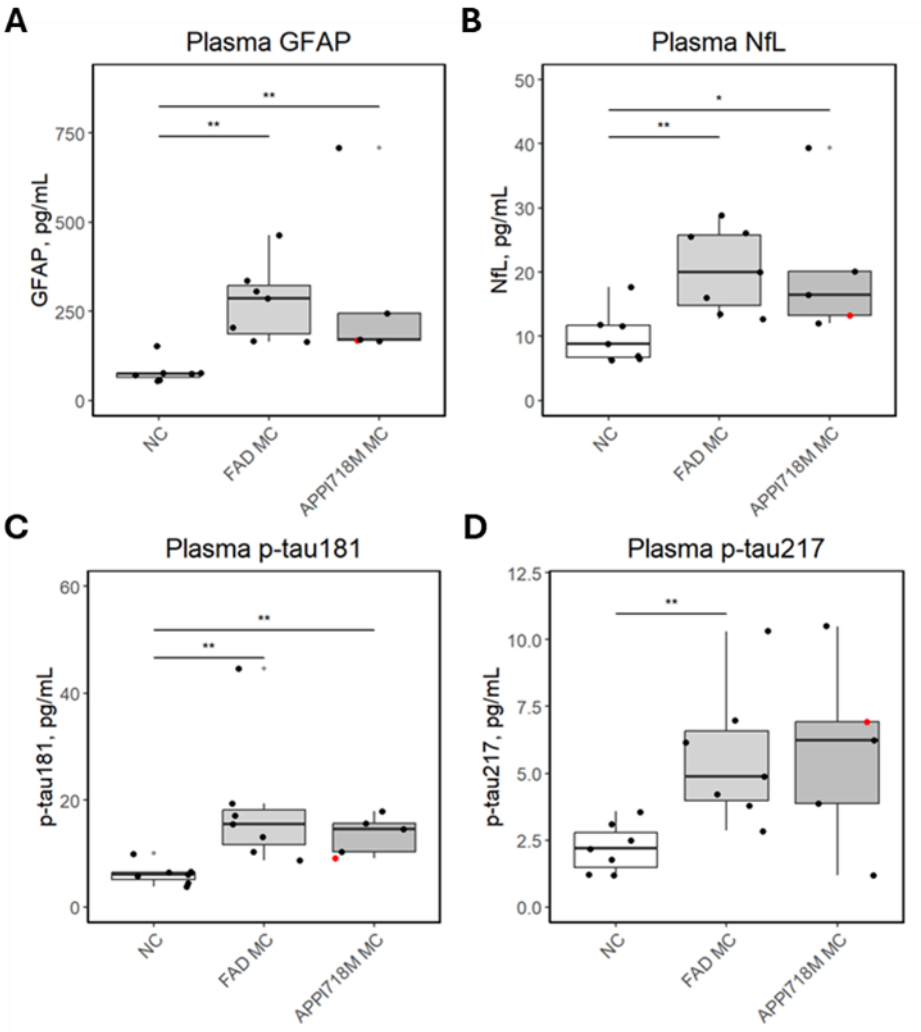
	APP p.I718M MC	FAD MC	NC controls
	N=5	N=7	N=7
Sex, F:M (%)	4:1 (80:20)	2:5 (29:71)	3:4 (43:57)
Age, y	59 (50-69)	59 (54-63)	54 (51-64)
Years from onset, y	2 (2-10)	2 (0-5)	
CDR	2 (0.5-3)**	0.5 (0.5-1)**	0 (0)
MMSE	16 (14-26)	21 (18-27)	29 (28-30)
APOE ε4+, N (%)	5 (100)[a]	1 (14)	4 (57)
2/4		1 (14)	
3/4	4 (80)		4 (57)
4/4	1 (20)		
Family, N (%)			
*APP*swe (p.KM670/671NL)		2 (29)	
*APP*arc (p.E693G)		4 (57)	
PSEN1 (p.H163Y)		1 (14)	
Plasma			
GFAP	171 (167-709)*	286 (164-463)*	76 (54-152)
NfL	17 (12-39)*	20 (13-29)*	9 (6-18)
p-tau217	6 (1-11)	5 (3-10) *	2 (1-4)
p-tau181	15 (9-18)*	16 (9-45)*	6 (4-10)

Age, years from onset, CDR, MMSE scores and plasma biomarker concentrations are expressed in median (range). All individuals were ≥50 years and all MC were affected with symptomatic AD (N=11) or mixed AD/DLB (N=1). NC controls were healthy non-carriers from the FAD study. Kruskal Wallis test, Mann-Whitney U and Fisher's exact T-test were used for significance testing. Reported p-values for plasma biomarkers in table were corrected for multiple comparisons (N=12). Statistical significance was indicated in comparisons of MC vs NC (* $p<0.05$, ** $p<0.01$) or *APP* p.I718M MC vs FAD MC ([a] $p<0.05$). CDR= Clinical Dementia Rating scale, GFAP= Glial fibrillary acidic protein, MMSE= Mini-mental state examination, MC= Mutation carriers, NC= Non-carriers, NfL= Neurofilament light chain.

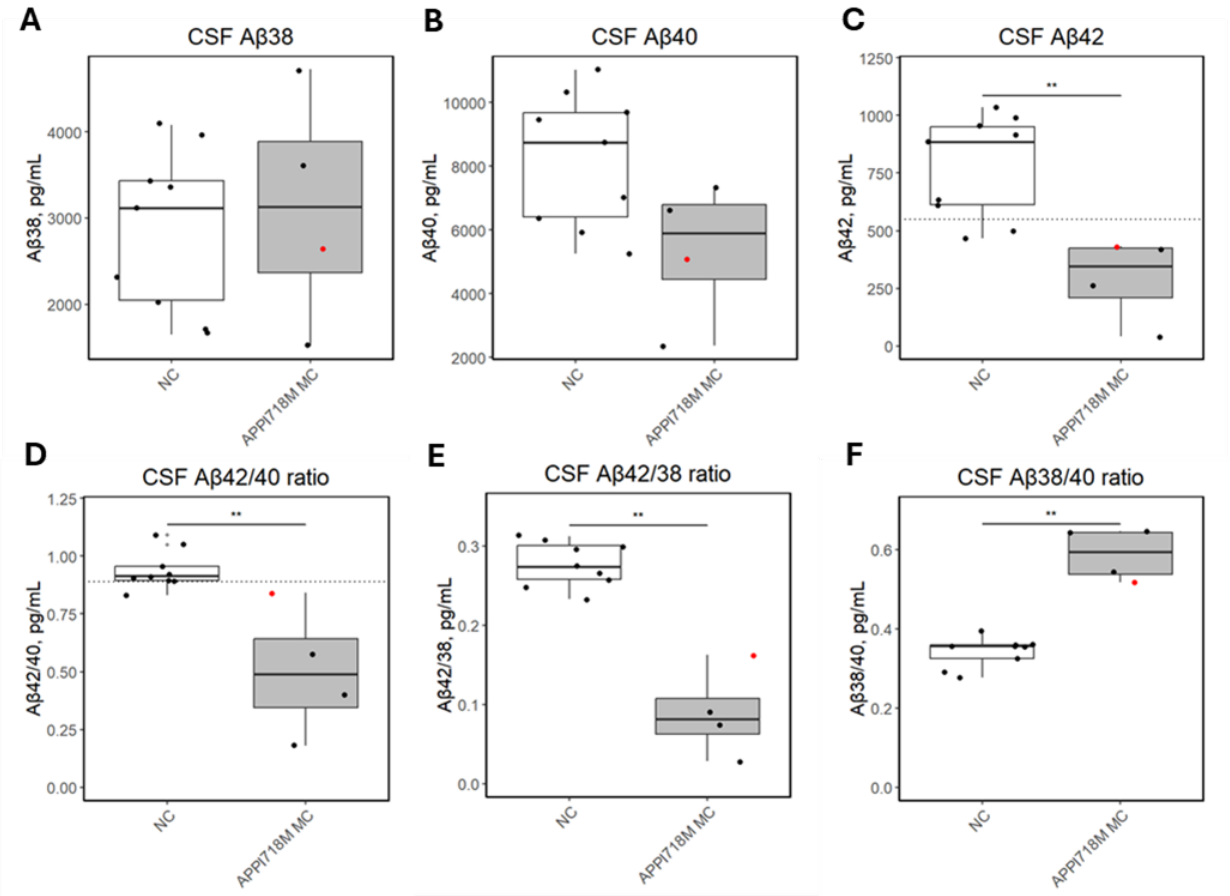
Supplementary Table 2. Clinical symptoms

	First symtom	Visuospatial	Dysexecutive	Language	Parkinsonism	Myoclonus	Hallucinations
III:1	Memory	Early	Early	Early*			Late
III:2	Memory	Early	Early	Late*	Early	Late	Early
III:3	Memory	Early		Late*	Late	Late	Late
III:4	Memory	Early	Early	Late			Late
III:5	Memory	Early	Early	Early*	Late	Late	

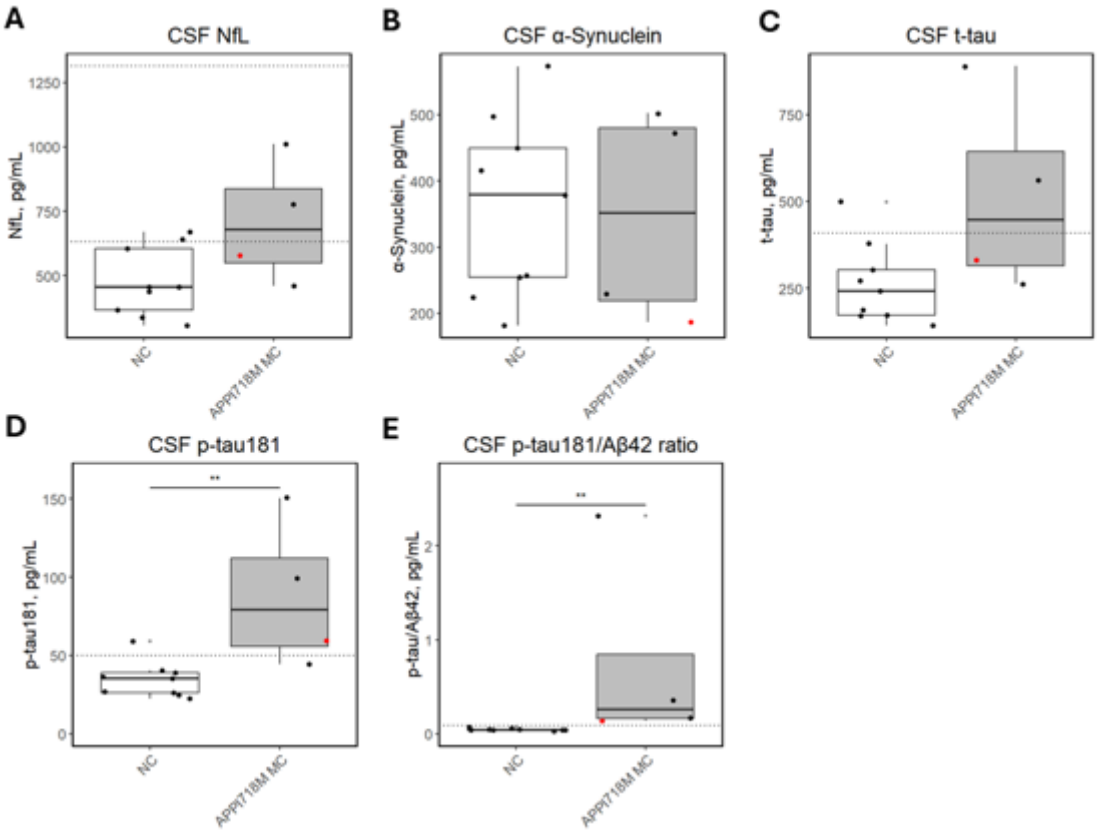
Clinical symptoms and neurological findings, as reported in medical journals. Parkinsonism includes bradykinesia, rigidity and tremor. The siblings fulfilled criteria of AD (III:1, III:2-III:5) or mixed AD/DLB (III:2). *Aphasia in advanced stage dementia in four individuals.



Supplementary Fig. 1. Plasma biomarkers, cross-sectional. Concentrations of (**A**) GFAP, (**B**) NfL, (**C**) p-tau181 and (**D**) p-tau217 in NC (N=7), FAD MC (N=7) and *APP* p.I718M MC (N=5). All individuals were >50 years of age. MC were symptomatic and affected by AD (N=11) or mixed AD/DLB (N=1, III:2). NC controls were healthy non-carriers from the FAD study. III:2 is annotated in red. *APP* p.I718M MC were sampled during initial memory investigation, except for the patient with extreme outlier concentrations in NfL and GFAP, who suffered from severe dementia (CDR=3) and was 10 years past onset. For the p-tau217 assay, imputation was performed in three individuals (III:4 and two NC) with values below the detection threshold. The low p-tau217 concentration in III:4 was identical in samples from two different occasions. Mann-Whitney U test was used for significance testing and p-values in figure were unadjusted for multiple comparisons. *p<0.05, **p<0.01. FAD=Familial Alzheimer disease study, MC=Mutation carriers, NC=Non-carriers.



Supplementary Fig. 2. CSF biomarkers, cross-sectional. Concentrations of (**A**) Aβ38, (**B**) Aβ40, (**C**) Aβ42, (**D**) Aβ42/40 ratio, (**E**) Aβ42/38 ratio and (**F**) Aβ38/40 ratio in NC (N=9) and symptomatic *APP* p.I718M MC (N=4). Reference intervals indicated when applicable, as detailed in manuscript. All individuals were >50 years of age. III:2 is annotated in red. NC controls were healthy non-carriers from the FAD study. Mann-Whitney U was used for significance testing and p-values in figure were unadjusted for multiple comparisons. *p<0.05, **p<0.01. MC=Mutation carriers, NC=Non-carriers.



Supplementary Fig. 3. CSF biomarkers, cross-sectional. Concentrations of (**A**) NfL, (**B**) α-Synuclein, (**C**) t-tau, (**D**) p-tau181 and (**E**) p-tau181/ Aβ42 ratio in NC (N=9) and symptomatic *APP* p.I718M MC (N=4). Reference intervals indicated when applicable, as detailed in manuscript. All individuals were >50 years of age. III:2 is annotated in red. NC controls were healthy non-carriers from the FAD study. Mann-Whitney U was used for significance testing and p-values in figure were unadjusted for multiple comparisons. *p<0.05, **p<0.01, ***p<0.001. MC=Mutation carriers, NC=Non-carriers.

HYMAN, B. T., PHELPS, C. H., BEACH, T. G., BIGIO, E. H., CAIRNS, N. J., CARRILLO, M. C., DICKSON, D. W., DUYCKAERTS, C., FROSCH, M. P., MASLIAH, E., MIRRA, S. S., NELSON, P. T., SCHNEIDER, J. A., THAL, D. R., THIES, B., TROJANOWSKI, J. Q., VINTERS, H. V. & MONTINE, T. J. 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement,* 8**,** 1-13.

MCKEITH, I. G., BOEVE, B. F., DICKSON, D. W., HALLIDAY, G., TAYLOR, J. P., WEINTRAUB, D., AARSLAND, D., GALVIN, J., ATTEMS, J., BALLARD, C. G., BAYSTON, A., BEACH, T. G., BLANC, F., BOHNEN, N., BONANNI, L., BRAS, J., BRUNDIN, P., BURN, D., CHEN-PLOTKIN, A., DUDA, J. E., EL-AGNAF, O., FELDMAN, H., FERMAN, T. J., FFYTCHE, D., FUJISHIRO, H., GALASKO, D., GOLDMAN, J. G., GOMPERTS, S. N., GRAFF-RADFORD, N. R., HONIG, L. S., IRANZO, A., KANTARCI, K., KAUFER, D., KUKULL, W., LEE, V. M. Y., LEVERENZ, J. B., LEWIS, S., LIPPA, C., LUNDE, A., MASELLIS, M., MASLIAH, E., MCLEAN, P., MOLLENHAUER, B., MONTINE, T. J., MORENO, E., MORI, E., MURRAY, M., O'BRIEN, J. T., ORIMO, S., POSTUMA, R. B., RAMASWAMY, S., ROSS, O. A., SALMON, D. P., SINGLETON, A., TAYLOR, A., THOMAS, A., TIRABOSCHI, P., TOLEDO, J. B., TROJANOWSKI, J. Q., TSUANG, D., WALKER, Z., YAMADA, M. & KOSAKA, K. 2017. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology,* 89**,** 88-100.

MCKHANN, G. M., KNOPMAN, D. S., CHERTKOW, H., HYMAN, B. T., JACK, C. R., JR., KAWAS, C. H., KLUNK, W. E., KOROSHETZ, W. J., MANLY, J. J., MAYEUX, R., MOHS, R. C., MORRIS, J. C., ROSSOR, M. N., SCHELTENS, P., CARRILLO, M. C., THIES, B., WEINTRAUB, S. & PHELPS, C. H. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement,* 7**,** 263-9.