

Supplementary Table S1. Summary of neuroimaging findings related to *MAPT* mutations

Reference	Modality	Study design	Population	Findings
Domínguez-Vivero et al. (2020)	Structural MRI	Cross-sectional	12 preclinical <i>MAPT</i> , 44 HC	Preclinical <i>MAPT</i> compared to HC showed symmetrical volume loss in the caudate, putamen, hippocampus, amygdala, nucleus accumbens, and several regions of the frontal and temporal lobes.
Olney et al. (2020)	Diffusion MRI	Cross-sectional	9 preclinical <i>MAPT</i> , 40 HC	No differences between carriers and controls.
	Structural MRI	Cross-sectional	35 presymptomatic <i>MAPT</i> , 12 mildly/questionably symptomatic <i>MAPT</i> , 20 symptomatic <i>MAPT</i> , 40 presymptomatic <i>C9orf72</i> , 19 mildly/questionably symptomatic <i>C9orf72</i> , 36 symptomatic <i>C9orf72</i> , 28 presymptomatic <i>GRN</i> , 12 mildly/questionably symptomatic <i>GRN</i> , 16 symptomatic <i>GRN</i> , 102 HC	Mildly/questionably symptomatic <i>MAPT</i> compared to HC showed volume loss in insula and medial temporal regions. Symptomatic <i>MAPT</i> showed atrophy in temporal regions bilaterally.
Chen et al. (2019a)	Diffusion MRI	Cross-sectional	12 presymptomatic <i>MAPT</i> , 10 symptomatic <i>MAPT</i> (5 bvFTD, 4 bvFTD with parkinsonism, 1 MCI), 20 HC	At baseline, presymptomatic carriers showed higher MD in entorhinal white matter, propagating to the limbic tracts and frontotemporal projections in symptomatic carriers.
		Longitudinal	10 presymptomatic <i>MAPT</i> , 6 symptomatic <i>MAPT</i> , 10 HC	All <i>MAPT</i> carriers showed an increased rate of entorhinal MD change compared to controls. Entorhinal white matter abnormalities precede symptom onset in carriers.
Chen et al. (2019b)	Structural MRI	Longitudinal	14 presymptomatic <i>MAPT</i> (4 converters; bvFTD, PSP, bvFTD with parkinsonism, MCI), 13 HC	No differences between carriers and controls at baseline, except in converters who showed lower volumes within the temporal, frontal and parietal lobes compared to controls and non-converter carriers.
Chen et al. (2019c)	¹ H MRS	Cross-sectional	9 presymptomatic <i>MAPT</i> , 10 symptomatic <i>MAPT</i> (5 bvFTD, 4 MCI, 1 PSP), 25 HC	Both symptomatic and presymptomatic <i>MAPT</i> had lower NAA/Cr and NAA/ml in the frontal lobe compared to HC.
Chen et al. (2019d)	¹ H MRS	Longitudinal	8 <i>MAPT</i> converters (2 bvFTD, 2 bvFTD with PSP, 1 bvFTD with parkinsonism, 3 MCI)	<i>MAPT</i> converters showed a trajectory of decreasing NAA/ml and increasing ml/Cr in inferior cingulate gyrus two years before symptom onset.
Mutsaerts et al. (2019)	ASL	Cross-sectional	18 presymptomatic <i>MAPT</i> , 34 presymptomatic <i>C9orf72</i> , 55 presymptomatic <i>GRN</i> , 113 HC	No differences in cerebral blood flow between presymptomatic <i>MAPT</i> and HC.
Panman et al. (2019)	Structural MRI	Cross-sectional	14 presymptomatic <i>MAPT</i> , 11 presymptomatic <i>C9orf72</i> , 33 presymptomatic <i>GRN</i> , 53 HC	Presymptomatic <i>MAPT</i> and HC had no gray matter differences at baseline. At follow up, carriers showed lower gray matter in the left temporal pole compared to controls.
		Longitudinal	14 presymptomatic <i>MAPT</i> , 11 presymptomatic <i>C9orf72</i> , 33 presymptomatic <i>GRN</i> , 53 HC	Presymptomatic <i>MAPT</i> compared to HC showed greater grey matter volume decline in the hippocampus.
	Diffusion MRI	Cross-sectional	14 presymptomatic <i>MAPT</i> , 12 presymptomatic <i>C9orf72</i> , 28 presymptomatic <i>GRN</i> , 50 HC	Presymptomatic <i>MAPT</i> and HC had no white matter differences at baseline or follow up.
		Longitudinal	14 presymptomatic <i>MAPT</i> , 12 presymptomatic <i>C9orf72</i> , 28 presymptomatic <i>GRN</i> , 50 HC	Presymptomatic <i>MAPT</i> compared to HC showed greater longitudinal FA decrease in predominantly left-sided frontotemporal tracts.

Tsai et al. (2019)	[¹⁸ F]flortaucipir PET	Cross-sectional	6 symptomatic <i>MAPT</i> , 5 symptomatic <i>C9orf72</i> , 1 symptomatic <i>GRN</i> , 10 bvFTD, 2 svPPA, 11 nfvPPA, 10 CBS, 53 HC	Tracer retention was highest in carriers with an "Alzheimer's-like" 3R/4R tau isoform, but was also seen in carriers with 4R tau isoforms.
Cash et al. (2018)	Structural MRI	Cross-sectional	23 presymptomatic <i>MAPT</i> , 10 <i>MAPT</i> -bvFTD, 40 presymptomatic <i>C9orf72</i> , 25 symptomatic <i>C9orf72</i> (18 bvFTD, 3 FTD-ALS, 2 nfvPPA, 1 svPPA, 1 other dementia), 65 presymptomatic <i>GRN</i> , 12 symptomatic <i>GRN</i> (5 bvFTD, 5 nfvPPA, 1 CBS), 144 HC	Presymptomatic <i>MAPT</i> compared to HC showed no volume differences. Symptomatic <i>MAPT</i> had bilateral atrophy in the amygdala, hippocampus, temporal lobes, insula, and orbitofrontal lobes.
Fumagalli et al. (2018)	Structural MRI	Cross-sectional	24 presymptomatic <i>MAPT</i> , 15 symptomatic <i>MAPT</i> , 42 presymptomatic <i>C9orf72</i> , 31 symptomatic <i>C9orf72</i> , 66 presymptomatic <i>GRN</i> , 17 symptomatic <i>GRN</i> , 148 HC	Presymptomatic <i>MAPT</i> compared to HC showed volume loss in the medial temporal region, and symptomatic <i>MAPT</i> symmetrical atrophy in anterior and medial temporal lobes.
Jiskoot et al. (2018)	Diffusion MRI	Cross-sectional	17 presymptomatic <i>MAPT</i> , 13 symptomatic <i>MAPT</i> , 35 presymptomatic <i>C9orf72</i> , 19 symptomatic <i>C9orf72</i> , 52 presymptomatic <i>GRN</i> , 4 symptomatic <i>GRN</i> , 115 HC	Presymptomatic <i>MAPT</i> compared to HC showed deficits in uncinate fasciculus, cingulum, superior longitudinal fasciculus, and superior corona radiata. Symptomatic <i>MAPT</i> showed internal capsule diffusivity changes.
Jones et al. (2018)	[¹⁸ F]AV-1451 PET	Cross-sectional	3 presymptomatic <i>MAPT</i> , 10 symptomatic <i>MAPT</i> , 241 HC	Higher binding in <i>MAPT</i> mutations associated with mixed 3R/4R isoform than in those associated with 4R isoform aggregates. Elevated uptake was observed also in presymptomatic carriers with these mutations.
Dopper et al. (2016)	ASL	Cross-sectional	11 presymptomatic <i>MAPT</i> , 23 presymptomatic <i>GRN</i> , 31 HC	No differences at baseline in cerebral blood flow between presymptomatic <i>MAPT</i> and HC.
		Longitudinal	11 presymptomatic <i>MAPT</i> , 23 presymptomatic <i>GRN</i> , 31 HC	No longitudinal differences between presymptomatic <i>MAPT</i> and HC.
Mahoney et al. (2015)	Diffusion MRI	Cross-sectional	8 <i>MAPT</i> -bvFTD, 4 <i>C9orf72</i> -bvFTD, 11 sporadic bvFTD, 18 HC	<i>MAPT</i> -bvFTD showed lower FA in right parahippocampal cingulum, and higher MD in right uncinate fasciculus and parahippocampal cingulum compared to controls.
		Longitudinal	8 <i>MAPT</i> -bvFTD, 4 <i>C9orf72</i> -bvFTD, 11 sporadic bvFTD, 18 HC	<i>MAPT</i> -bvFTD showed the largest FA reductions within left uncinate fasciculus.
Rohrer et al. (2015)	Structural MRI	Cross-sectional	24 presymptomatic or symptomatic <i>MAPT</i> , 33 presymptomatic or symptomatic <i>C9orf72</i> , 52 presymptomatic or symptomatic <i>GRN</i> , 93 HC	<i>MAPT</i> carriers showed volume loss in the hippocampus and amygdala at 15 years before expected onset, temporal lobe at 10 years before expected onset, and insula at 5 years before expected onset.
Whitwell et al. (2015)	Structural MRI	Longitudinal	21 symptomatic <i>MAPT</i> (19 bvFTD, 1 FTD-ALS, 1 PPA), 11 symptomatic <i>C9orf72</i> (7 bvFTD, 3 FTD-ALS, 1 AD), 11 symptomatic <i>GRN</i> (6 bvFTD, 4 PPA, 1 AD), 15 sporadic bvFTD	Symptomatic <i>MAPT</i> compared to HC had greatest regional rates of atrophy in frontal and temporal lobes, specifically in temporal pole. Symptomatic <i>MAPT</i> and <i>C9orf72</i> had slowest overall rates of atrophy among all groups.
Deters et al. (2014)	Structural MRI	Cross-sectional	3 presymptomatic <i>MAPT</i> , 8 <i>MAPT</i> -bvFTD, 8 HC	Presymptomatic and symptomatic <i>MAPT</i> both showed bilateral volume loss in the medial temporal lobes compared to HC.

	[¹⁸ F]FDG-PET	Cross-sectional	3 presymptomatic <i>MAPT</i> , 8 <i>MAPT</i> -bvFTD, 8 HC	Symptomatic <i>MAPT</i> compared to HC showed reduced metabolism in the medial temporal lobes and prefrontal cortex. Presymptomatic <i>MAPT</i> showed an intermediate level of glucose metabolism between those of symptomatic carriers and controls, with reductions focused to the medial temporal lobes.
Dopper et al. (2014)	Diffusion MRI	Cross-sectional	9 presymptomatic <i>MAPT</i> , 27 presymptomatic <i>GRN</i> , 38 HC	Presymptomatic <i>MAPT</i> compared to HC showed decreased FA and increased MD, RD, and AXD in widespread frontotemporal white matter tracts.
	Task-free fMRI	Cross-sectional	10 presymptomatic <i>MAPT</i> , 27 presymptomatic <i>GRN</i> , 38 HC	Presymptomatic <i>MAPT</i> compared to HC showed no alterations in connectivity of right frontoinsula, anterior midcingulate cortex, posterior cingulate cortex.
Lant et al. (2014)	[¹¹ C](R)-PK11195 PET	Cross-sectional	78 pathologically confirmed cases of FTLT (10 <i>MAPT</i> , 8 <i>GRN</i> , 9 <i>C9orf72</i>), 13 AD, 13 HC	Microglial cell activation in temporal subcortical white matter was significantly higher in <i>MAPT</i> -FTLD than in other genetic (<i>GRN</i> , <i>C9orf72</i>) or non-genetic forms of FTLT.
Mahoney et al. (2014)	Diffusion MRI	Cross-sectional	9 symptomatic <i>MAPT</i> (bvFTD), 4 symptomatic <i>C9orf72</i> (3 bvFTD, 1 bvFTD-MND), 14 sporadic FTD (2 bvFTD-PSP, 1 bvFTD-MND, 1 bvFTD-CBS), 25 AD, 20 HC	Symptomatic <i>MAPT</i> compared to HC had consistent alterations in left uncinate fasciculus across diffusivity metrics. Symptomatic <i>MAPT</i> compared to symptomatic <i>C9orf72</i> also showed reduced FA within the left anterior temporal pole, and altered RD and TR within the corticospinal tract, anterior thalamic radiation, inferior longitudinal fasciculus, and uncinate fasciculus compared to AD.
Whitwell et al. (2012)	Structural MRI	Cross-sectional	25 <i>MAPT</i> -bvFTD, 12 <i>GRN</i> -bvFTD, 19 <i>C9orf72</i> -bvFTD (2 with ALS), 20 sporadic FTD (7 with ALS), 40 HC	Symptomatic <i>MAPT</i> showed striking anteromedial temporal atrophy compared to controls and <i>C9orf72</i> -bvFTD.
Rohrer et al. (2011a)	Structural MRI	Cross-sectional	14 symptomatic <i>MAPT</i> (12 bvFTD, 2 CBS), 35 HC	Symptomatic <i>MAPT</i> compared to HC showed symmetrical atrophy predominantly in the anterior, medial, and inferior temporal cortices, with less involvement of the insula and orbitofrontal cortices.
Seelaar et al. (2011)	SPECT	Cross-sectional	10 symptomatic <i>MAPT</i> (9 bvFTD, 1 bvFTD with parkinsonism), 10 HC	Symptomatic <i>MAPT</i> compared to HC showed hypoperfusion in frontal, temporal, and parietal lobes.
Whitwell et al. (2011)	Structural MRI	Cross-sectional	8 presymptomatic <i>MAPT</i> , 8 HC	No difference in gray matter volumes compared to controls.
	Task-free fMRI	Cross-sectional	8 presymptomatic <i>MAPT</i> , 8 HC	Presymptomatic <i>MAPT</i> compared to HC showed reduced DMN connectivity between precuneus, lateral temporal lobes and medial prefrontal cortex, and increased connectivity between precuneus and medial parietal lobe. No differences were found in frontoinsular seed connectivity compared to controls.
Kantarci et al. (2010)	Structural MRI	Cross-sectional	14 presymptomatic <i>MAPT</i> , 10 symptomatic <i>MAPT</i> (8 FTD, 1 FTD with parkinsonism, 1 PPND), 24 HC	Symptomatic <i>MAPT</i> compared to HC showed lower hippocampal volumes.
	¹ H MRS	Cross-sectional	14 presymptomatic <i>MAPT</i> , 10 symptomatic <i>MAPT</i> (8 FTD, 1 FTD with parkinsonism, 1 PPND), 24 HC	Presymptomatic <i>MAPT</i> compared to HC had elevated mI/Cr and decreased NAA/mI in posterior cingulate gyrus. Symptomatic carriers showed also decreased NAA/Cr.
Miyoshi et al. (2010)	[¹¹ C]DAA1106 PET	Cross-sectional	3 presymptomatic <i>MAPT</i> , 9 HC	All carriers showed increased glial activities in varying cortical regions.
	l-[β- ¹¹ C]dopa PET	Cross-sectional	3 presymptomatic <i>MAPT</i> , 10 HC	All carriers showed low dopamine synthesis in the putamen.

	[¹¹ C]MP4A PET	Cross-sectional	3 presymptomatic <i>MAPT</i> , 10 HC	One carrier exhibited reduced cortical acetylcholinesterase activity, and one showed increased acetylcholinesterase activity in the hippocampus and posterior cingulate cortex.
Rohrer et al. (2010)	Structural MRI	Cross-sectional	11 symptomatic <i>MAPT</i> (bvFTD), 9 symptomatic <i>GRN</i> (4 bvFTD, 3 PPA, 1 PPA/CBS, 1 CBS), 15 HC	Symptomatic <i>MAPT</i> compared to HC showed symmetrical atrophy in anteromedial temporal lobes, orbitofrontal cortex and ventral insula with less involvement of the anterior cingulate.
		Longitudinal	6 symptomatic <i>MAPT</i> (bvFTD), 4 symptomatic <i>GRN</i>	Symptomatic <i>MAPT</i> compared to HC showed longitudinal volume loss symmetrically in the anteromedial temporal lobes, orbitofrontal cortex and white matter tracts including the corpus callosum.
Whitwell et al. (2009a)	Structural MRI	Cross-sectional	22 symptomatic <i>MAPT</i> (12 bvFTD, 6 bvFTD with parkinsonism, 1 PPA), 19 HC	Symptomatic <i>MAPT</i> compared to HC showed gray matter loss in the anterior temporal lobes with varying degrees of involvement of the frontal and parietal lobes. Subjects with IVS10+16, IVS10+3, N279K, and S305N mutations showed gray matter loss focused to the medial temporal lobes and subjects with P301L or V337M mutations gray matter loss focused to the lateral temporal lobes.
Whitwell et al. (2009b)	Structural MRI	Cross-sectional	12 symptomatic <i>MAPT</i> (2 bvFTD, 5 bvFTD with parkinsonism, 2 PPA, 1 AD, 2 MCI), 12 symptomatic <i>GRN</i> (5 bvFTD, 1 bvFTD with parkinsonism, 2 PPA, 1 AD, 1 PD, 2 MCI), 24 HC	Symptomatic <i>MAPT</i> showed atrophy predominantly in the anteromedial temporal lobes compared to both controls and symptomatic <i>GRN</i> .
Arvanitakis et al. (2007)	Structural MRI	Cross-sectional	2 presymptomatic <i>MAPT</i> , 5 symptomatic <i>MAPT</i> (PPND)	All symptomatic and one presymptomatic <i>MAPT</i> had temporal lobe atrophy.
	[¹⁸ F]FDG-PET	Cross-sectional	2 presymptomatic <i>MAPT</i> , 5 symptomatic <i>MAPT</i> (PPND)	All carriers showed asymmetric temporal lobe hypometabolism. Several presymptomatic and symptomatic carriers additionally showed medial temporal and frontal lobe hypometabolism

FTLD, frontotemporal lobar degeneration; FTD, frontotemporal dementia; bvFTD, behavioral variant FTD; PPA, primary progressive aphasia; svPPA, semantic variant of PPA; nvPPA, nonfluent variant PPA; CBS, corticobasal syndrome; MND, motor neurone disease; PSP, progressive supranuclear palsy; AD, Alzheimer's disease; PD, Parkinson's disease; MCI, mild cognitive impairment; PPND, pallido-ponto-nigral degeneration; HC, healthy control; DMN, default mode network; FA, fractional anisotropy; MD, mean diffusivity; AXD, axial diffusivity; RD, radial diffusivity; TR, trace diffusivity; NAA, N-acetylaspartate; Cr, creatine; mI, myoinositol