

Supplementary Table S2. Summary of neuroimaging findings related to *GRN* mutations

Reference	Modality	Study design	Population	Findings
Chen et al. (2020)	Structural MRI	Cross-sectional	8 presymptomatic <i>GRN</i> , 5 symptomatic <i>GRN</i> (1 MCI, 1 MCI who progressed to bvFTD, 1 bvFTD, 1 PPA and CBS, 1 atypical FTLD with right parietal lobe syndrome), 10 HC	At baseline, presymptomatic <i>GRN</i> compared to HC showed lower frontal and occipital lobar volumes. Symptomatic carriers showed lower frontal, parietal and occipital lobar volumes.
		Longitudinal	6 presymptomatic <i>GRN</i> , 5 symptomatic <i>GRN</i> (1 MCI, 1 MCI who progressed to bvFTD, 1 bvFTD, 1 PPA and CBS, 1 atypical FTLD with right parietal lobe syndrome), 10 HC	Presymptomatic <i>GRN</i> showed longitudinal volume loss in frontal and parietal lobes. Symptomatic carriers showed decline also in temporal lobe volume.
Olney et al. (2020)	Structural MRI	Cross-sectional	28 presymptomatic <i>GRN</i> , 12 mildly/questionably symptomatic <i>GRN</i> , 16 symptomatic <i>GRN</i> , 40 presymptomatic <i>C9orf72</i> , 19 mildly/questionably symptomatic <i>C9orf72</i> , 36 symptomatic <i>C9orf72</i> , 35 presymptomatic <i>MAPT</i> , 12 mildly/questionably symptomatic <i>MAPT</i> , 20 symptomatic <i>MAPT</i> , 102 HC	Around half presymptomatic <i>GRN</i> showed volume loss compared to HC in posterior temporal and parietal regions, most <i>GRN</i> carriers with mild/questionable impairment in the frontal region, and most <i>GRN</i> carriers with FTLD in varying regions.
Benussi et al. (2019)	Structural MRI	Cross-sectional	48 presymptomatic <i>GRN</i> , 51 symptomatic <i>GRN</i> , 4 presymptomatic <i>C9orf72</i> , 10 symptomatic <i>C9orf72</i> , 73 HC	Presymptomatic <i>GRN</i> compared to HC showed a significant increase in WMH on estimate 20 years before expected symptom onset.
Lee et al. (2019)	Structural MRI	Cross-sectional	14 presymptomatic <i>GRN</i> , 3 <i>GRN</i> -MCI, 30 HC	Preclinical <i>GRN</i> compared to HC showed no significant differences.
	Task-free fMRI	Cross-sectional	13 presymptomatic <i>GRN</i> , 2 <i>GRN</i> -MCI, 8 symptomatic <i>GRN</i> (4 bvFTD, 3 AD-type dementia, 1 CBS), 30 HC	Preclinical <i>GRN</i> compared to HC showed hyperconnectivity in SN, nfvPPA, CBS and DMN networks, which for all four networks converged in thalamic regions. Whole-brain degree analysis suggested thalamic hyperconnectivity in preclinical and hypoconnectivity in symptomatic carriers.
Mutsaerts et al. (2019)	ASL	Cross-sectional	34 presymptomatic <i>C9orf72</i> , 18 presymptomatic <i>MAPT</i> , 55 presymptomatic <i>GRN</i> , 113 HC	No significant effects in the <i>GRN</i> subgroup.
Panman et al. (2019)	Structural MRI	Cross-sectional	33 presymptomatic <i>GRN</i> , 11 presymptomatic <i>C9orf72</i> , 14 presymptomatic <i>MAPT</i> , 53 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
		Longitudinal	33 presymptomatic <i>GRN</i> , 11 presymptomatic <i>C9orf72</i> , 14 presymptomatic <i>MAPT</i> , 53 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
	Diffusion MRI	Cross-sectional	28 presymptomatic <i>GRN</i> , 12 presymptomatic <i>C9orf72</i> , 14 presymptomatic <i>MAPT</i> , 50 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
		Longitudinal	28 presymptomatic <i>GRN</i> , 12 presymptomatic <i>C9orf72</i> , 14 presymptomatic <i>MAPT</i> , 50 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
Sudre et al. (2019)	Structural MRI	Cross-sectional	101 presymptomatic <i>GRN</i> , 32 symptomatic <i>GRN</i> , 203 HC	Presymptomatic <i>GRN</i> compared to HC had higher WMH burden in occipital and parietal lobes, and symptomatic carriers in frontal and occipital lobes. WMH burden in a lobe was associated with smaller GM volume across all carriers.
		Longitudinal	39 presymptomatic <i>GRN</i> , 12 symptomatic <i>GRN</i> , 73 HC	Symptomatic <i>GRN</i> compared to presymptomatic carriers showed greater WMH accrual in the medial region.

Alexander et al. (2018)	Structural MRI	Cross-sectional	2 unaffected <i>GRN</i> , 3 <i>GRN</i> -CSND, 11 controls (9 unaffected, 2 CSND)	No significant difference between predementia <i>GRN</i> and HC.
	Task-based fMRI	Cross-sectional	2 unaffected <i>GRN</i> , 3 <i>GRN</i> -CSND, 11 controls (9 unaffected, 2 CSND)	Predementia <i>GRN</i> compared to HC showed lower lateral prefrontal activation during a relational reasoning task.
Cash et al. (2018)	Structural MRI	Cross-sectional	65 presymptomatic <i>GRN</i> , 12 symptomatic <i>GRN</i> (5 bvFTD, 5 nvPPA, 1 CBS), 40 presymptomatic <i>C9orf72</i> , 25 symptomatic <i>C9orf72</i> (18 bvFTD, 3 FTD-ALS, 2 nvPPA, 1 svPPA, 1 other dementia), 23 presymptomatic <i>MAPT</i> , 10 <i>MAPT</i> -bvFTD, 144 HC	Presymptomatic <i>GRN</i> compared to HC showed reduced volume in posterior frontal and parietal lobes and striatum. Symptomatic <i>GRN</i> showed lower grey matter volume in the frontal lobe, insula, anterior cingulate, superior and middle temporal gyri, striatum, and more posteriorly in the lateral and medial parietal lobes.
Fumagalli et al. (2018)	Structural MRI	Cross-sectional	66 presymptomatic <i>GRN</i> , 17 symptomatic <i>GRN</i> , 42 presymptomatic <i>C9orf72</i> , 31 symptomatic <i>C9orf72</i> , 24 presymptomatic <i>MAPT</i> , 15 symptomatic <i>MAPT</i> , 148 HC	Symptomatic <i>GRN</i> compared to HC showed asymmetric frontal and parietal volume loss. Presymptomatic <i>GRN</i> did not show differences.
Gazzina et al. (2018)	Structural MRI	Cross-sectional	19 presymptomatic <i>GRN</i> , 17 HC	Presymptomatic <i>GRN</i> compared to HC showed increased cortical thickness and decreased surface area in the right parietal lobe.
Jiskoot et al. (2018)	Diffusion MRI	Cross-sectional	52 presymptomatic <i>GRN</i> , 4 symptomatic <i>GRN</i> , 35 presymptomatic <i>C9orf72</i> , 19 symptomatic <i>C9orf72</i> , 17 presymptomatic <i>MAPT</i> , 13 symptomatic <i>MAPT</i> , 115 HC	Presymptomatic <i>GRN</i> compared to HC showed reduced integrity particularly in the internal capsule. Most tracts showed significant left-right differences.
Olm et al. (2018)	Structural MRI	Cross-sectional	11 presymptomatic <i>GRN</i> , 15 symptomatic <i>GRN</i> (6 bvFTD, 4 CBS, 3 nvPPA, 1 svPPA, 1 AD), 34 HC	Presymptomatic <i>GRN</i> compared to HC showed reduced grey matter density in bilateral orbitofrontal, insular and anterior temporal cortex. Symptomatic carriers showed reduced grey matter in bilateral frontal, temporal, parietal and occipital lobes and posterior cingulate.
		Longitudinal	11 presymptomatic <i>GRN</i> , 15 symptomatic <i>GRN</i> (6 bvFTD, 4 CBS, 3 nvPPA, 1 svPPA, 1 AD), 34 HC	Presymptomatic <i>GRN</i> compared to HC showed greater annualized change in right orbitofrontal cortex and left occipital cortex.
	Diffusion MRI	Cross-sectional	11 presymptomatic <i>GRN</i> , 9 symptomatic <i>GRN</i> , 34 HC	Presymptomatic <i>GRN</i> compared to HC showed reduced FA in bilateral superior longitudinal fasciculus, left corticospinal tract, and frontal corpus callosum. Symptomatic carriers showed white-matter damage in most major association tracts and in frontal, temporal, parietal and occipital subcortical white matter.
		Longitudinal	10 presymptomatic <i>GRN</i> , 9 symptomatic <i>GRN</i> , 32 HC	Presymptomatic <i>GRN</i> compared to HC showed greater annualized FA reduction in right superior longitudinal fasciculus and right frontal corpus callosum.
Popuri et al. (2018)	Structural MRI	Cross-sectional	9 presymptomatic <i>GRN</i> , 15 presymptomatic <i>C9orf72</i> , 37 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
Sudre et al. (2017)	Structural MRI	Cross-sectional	25 presymptomatic <i>GRN</i> , 7 symptomatic <i>GRN</i> , 28 presymptomatic <i>C9orf72</i> , 23 symptomatic <i>C9orf72</i> , 8 presymptomatic <i>MAPT</i> , 13 symptomatic <i>MAPT</i> , 76 HC	Presymptomatic <i>GRN</i> showed a significant association between WMH volume and years from expected age of onset. Symptomatic compared to presymptomatic <i>GRN</i> mutation carriers had more WMH in frontal and occipital lobes.

Ameur et al. (2016)	Structural MRI	Cross-sectional	11 <i>GRN</i> -bvFTD, 17 <i>C9orf72</i> -bvFTD, 11 HC	5/11 <i>GRN</i> -bvFTD patients had extensive frontal white-matter lesions that was associated with greater atrophy. The grade of lesions was higher compared to HC and <i>C9orf72</i> -bvFTD.
Dopper et al. (2016)	ASL	Cross-sectional	23 presymptomatic <i>GRN</i> , 11 presymptomatic <i>MAPT</i> , 31 HC	At follow-up, presymptomatic <i>GRN</i> compared with HC showed hypoperfusion in frontoparietal regions and and thalamus.
		Longitudinal	23 presymptomatic <i>GRN</i> , 11 presymptomatic <i>MAPT</i> , 31 HC	Presymptomatic <i>GRN</i> compared to HC showed greater longitudinal decline in frontal, temporal, parietal and subcortical areas.
Paternicò et al. (2016)	Structural MRI	Cross-sectional	11 presymptomatic <i>GRN</i> , 14 symptomatic <i>GRN</i> (7 bvFTD, 5 PPA, 2 CBS), 28 sporadic FTD (14 bvFTD, 10 PPA, 4 CBS), 26 HC	Patients with <i>GRN</i> -FTD had greater WMH burden than HC and sporadic FTD. WMHs were concentrated in the right middle frontal and superior temporal gyri and left superior frontal and parietal gyri.
Premi et al. (2016)	Structural MRI	Cross-sectional	17 presymptomatic <i>GRN</i> , 14 symptomatic <i>GRN</i> (7 bvFTD, 7 nvPPA), 33 HC	<i>GRN</i> -FTD and HC were distinguished by grey matter loss (particularly frontotemporal and parietal regions), presymptomatic <i>GRN</i> and HC were not.
	Diffusion MRI	Cross-sectional	17 presymptomatic <i>GRN</i> , 14 symptomatic <i>GRN</i> (7 bvFTD, 7 nvPPA), 33 HC	<i>GRN</i> -FTD and HC were distinguished by white matter alterations (particularly frontotemporal tracts), presymptomatic <i>GRN</i> carriers and HC were not.
	Task-free fMRI	Cross-sectional	17 presymptomatic <i>GRN</i> , 14 symptomatic <i>GRN</i> (7 bvFTD, 7 nvPPA), 33 HC	<i>GRN</i> -FTD and HC were distinguished by DC, ALFF, fALFF, ReHo, VMHC and network alterations (particularly SN and FPN). Classification of presymptomatic <i>GRN</i> and HC was most accurate based on local functional connectivity changes in frontoparietal and prefrontal areas.
Caroppo et al. (2015b)	Structural MRI	Cross-sectional	16 presymptomatic <i>GRN</i> , 17 HC	No significant difference between <i>GRN</i> carriers and HC.
		Longitudinal	14 presymptomatic <i>GRN</i> , 14 HC	Presymptomatic <i>GRN</i> at baseline compared to the same subjects 20-months later showed cortical thinning in left middle and inferior temporal gyri.
	[¹⁸ F]FDG-PET	Cross-sectional	16 presymptomatic <i>GRN</i> , 17 HC	At baseline, presymptomatic <i>GRN</i> compared to HC had hypometabolism in the left middle temporal gyrus.
		Longitudinal	14 presymptomatic <i>GRN</i> , 14 HC	Presymptomatic <i>GRN</i> compared to HC showed greater metabolism decrease in the frontal and temporal lobes and thalamus.
Rohrer et al. (2015)	Structural MRI	Cross-sectional	52 presymptomatic or symptomatic <i>GRN</i> , 24 presymptomatic or symptomatic <i>MAPT</i> , 33 presymptomatic or symptomatic <i>C9orf72</i> , 93 HC	Presymptomatic <i>GRN</i> showed volume loss in the insula approximately at 15 years before expected symptom onset, followed by temporal and parietal lobes. Striatal involvement and asymmetry emerged 5 years before expected onset.
Whitwell et al. (2015)	Structural MRI	Longitudinal	11 symptomatic <i>GRN</i> (6 bvFTD, 4 PPA, 1 AD), 11 symptomatic <i>C9orf72</i> (7 bvFTD, 3 FTD-ALS, 1 AD), 21 symptomatic <i>MAPT</i> (19 bvFTD, 1 FTD-ALS, 1 PPA), 15 sporadic bvFTD	Symptomatic <i>GRN</i> showed faster rates of volume loss than sporadic, <i>C9orf72</i> or <i>MAPT</i> groups in all four lobes. Regional rates were highest in frontal, temporal lobes, and parietal lobes.
Dopper et al. (2014)	Diffusion MRI	Cross-sectional	27 presymptomatic <i>GRN</i> , 9 presymptomatic <i>MAPT</i> , 38 HC	Presymptomatic <i>GRN</i> compared to HC showed no significant difference.
	Task-free fMRI	Cross-sectional	27 presymptomatic <i>GRN</i> , 10 presymptomatic <i>MAPT</i> , 38 HC	Presymptomatic <i>GRN</i> compared to HC showed connectivity reductions and increases associated with SN and reductions with DMN.

Pievani et al. (2014)	Structural MRI	Cross-sectional	5 presymptomatic <i>GRN</i> , 5 HC	Presymptomatic <i>GRN</i> compared to HC showed lower cortical thickness in the left middle frontal gyrus and right lateral orbitofrontal cortex and precentral gyrus.
	Diffusion MRI	Cross-sectional	5 presymptomatic <i>GRN</i> , 5 HC	Presymptomatic <i>GRN</i> compared to HC showed increased AXD in the right cingulum, superior longitudinal fasciculus and corticospinal tract.
	Task-free fMRI	Cross-sectional	5 presymptomatic <i>GRN</i> , 5 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
Premi et al. (2014)	Task-free fMRI	Cross-sectional	17 presymptomatic <i>GRN</i> , 14 symptomatic <i>GRN</i> (7 bvFTD, 7 nvPPA), 14 HC	Presymptomatic <i>GRN</i> compared to HC showed reduced ReHo in the left parietal region and increased ReHo in frontal regions. Connectivity modulations in symptomatic carriers included reduced ReHo, fALFF and DC in inferior parietal, frontal lobes and posterior cingulate cortex.
Bozzali et al. (2013)	Structural MRI	Cross-sectional	6 <i>GRN</i> -FTLD (4 bvFTD, 2 nvPPA), 17 sporadic FTLD (10 bvFTD, 7 nvPPA), 12 HC	<i>GRN</i> -FTLD compared to sporadic FTLD showed additional grey matter loss in the left prefrontal cortex.
	Diffusion MRI	Cross-sectional	6 <i>GRN</i> -FTLD (4 bvFTD, 2 nvPPA), 17 sporadic FTLD (10 bvFTD, 7 nvPPA), 12 HC	Within corpus callosum, <i>GRN</i> -FTLD compared to sporadic FTLD showed reduced FA and increased MD in the most anterior part.
Jacova et al. (2013)	Structural MRI	Cross-sectional	4 asymptomatic <i>GRN</i> , 5 <i>GRN</i> -CSND, 11 controls (8 asymptomatic, 3 CSND)	No significant difference between predementia <i>GRN</i> and HC.
	[¹⁸ F]FDG-PET	Cross-sectional	4 asymptomatic <i>GRN</i> , 5 <i>GRN</i> -CSND, 11 controls (8 asymptomatic, 3 CSND)	Asymptomatic and CSND- <i>GRN</i> showed right anterior cerebral hypometabolism compared to HC.
Moreno et al. (2013)	Structural MRI	Cross-sectional	13 presymptomatic <i>GRN</i> , 13 HC	Presymptomatic <i>GRN</i> showed pronounced age-related thinning of the temporal cortex.
Borroni et al. (2012)	Structural MRI	Cross-sectional	9 presymptomatic <i>GRN</i> , 7 <i>GRN</i> -FTLD (4 fvFTD, 3 nvPPA), 16 sporadic FTLD (9 fvFTD, 7 nvPPA), 24 HC	<i>GRN</i> -FTLD compared to sporadic FTLD showed reduction of grey matter volume in the left frontal cortex. Presymptomatic carriers did not differ from HC.
	Task-free fMRI	Cross-sectional	9 presymptomatic <i>GRN</i> , 7 <i>GRN</i> -FTLD (4 fvFTD, 3 nvPPA), 16 sporadic FTLD (9 fvFTD, 7 nvPPA), 24 HC	Presymptomatic <i>GRN</i> compared to HC showed increased connectivity within SN.
Whitwell et al. (2012)	Structural MRI	Cross-sectional	12 <i>GRN</i> -bvFTD, 19 <i>C9orf72</i> -bvFTD (2 with ALS), 25 <i>MAPT</i> -bvFTD, 20 sporadic FTD (7 with ALS), 40 HC	<i>GRN</i> -bvFTD compared to HC showed volume loss in temporoparietal regions, and showed higher asymmetry than other bvFTD subtypes.
Rohrer et al. (2010)	Structural MRI	Cross-sectional	9 symptomatic <i>GRN</i> (4 bvFTD, 3 PPA, 1 PPA/CBS, 1 CBS), 11 symptomatic <i>MAPT</i> (bvFTD), 15 HC	Symptomatic <i>GRN</i> compared to HC showed lower grey matter volume asymmetrically in inferior frontal lobe, dorsal insula, superior and middle temporal gyri, dorsal anterior cingulate cortex, precuneus and inferior parietal lobe. White matter volume was reduced in long intrahemispheric association tracts, the corpus callosum and brainstem tracts.
		Longitudinal	4 symptomatic <i>GRN</i> , 6 symptomatic <i>MAPT</i> (bvFTD)	Symptomatic <i>GRN</i> showed asymmetrical longitudinal volume loss involving mainly the inferior frontal, superior temporal, and inferior parietal lobes, precuneus and cingulate cortex, and in the white matter of long intrahemispheric association tracts.
Cruchaga et al. (2009)	Structural MRI	Cross-sectional	3 presymptomatic <i>GRN</i> , 1 <i>GRN</i> -PPA, 15 HC	<i>GRN</i> mutation carriers compared to HC had grey matter loss in frontal, temporal and posterior parietal areas, more prominent on the left.

	[¹⁸ F]FDG-PET	Cross-sectional	3 presymptomatic <i>GRN</i> , 1 <i>GRN</i> -PPA, 2 HC	<i>GRN</i> mutation carriers compared to HC showed hypometabolism in regions concordant with grey matter loss.
	Task-based fMRI	Cross-sectional	3 presymptomatic <i>GRN</i> , 1 <i>GRN</i> -PPA, 15 HC	<i>GRN</i> mutation carriers compared to HC had additional fMRI activation in the left prefrontal cortex and bilateral anterior insulae during semantic and phonemic covert word generation, and in the mesial prefrontal and anterior temporal cortex during word listening tasks.
Whitwell et al. (2009b)	Structural MRI	Cross-sectional	12 symptomatic <i>GRN</i> (5 bvFTD, 1 bvFTD with parkinsonism, 2 PPA, 1 AD, 1 PD, 2 MCI), 12 symptomatic <i>MAPT</i> (2 bvFTD, 5 bvFTD with parkinsonism, 2 PPA, 1 AD, 2 MCI), 24 HC	Symptomatic <i>GRN</i> compared to HC showed predominant volume loss in posterior temporal regions, with severe involvement of parietal lobes and additional involvement of the posterior cingulate gyrus and precuneus.
Beck et al. (2008)	Structural MRI	Cross-sectional	8 symptomatic <i>GRN</i> (4 bvFTD, 2 nvfPPA, 1 nvfPPA/SD, 1 nvfPPA/CBS), 9 symptomatic <i>MAPT</i> (bvFTD, nvfPPA or CBS), 8 sporadic FTLD-U (svPPA), HC	Symptomatic <i>GRN</i> compared to HC showed strikingly asymmetrical volume loss in the frontal, temporal and parietal lobes. Carriers showed more asymmetry than in other FTLD groups.
Borroni et al. (2008)	Structural MRI	Cross-sectional	7 presymptomatic <i>GRN</i> , 25 HC	No significant difference between presymptomatic <i>GRN</i> and HC.
	Diffusion MRI	Cross-sectional	7 presymptomatic <i>GRN</i> , 25 HC	Presymptomatic <i>GRN</i> compared to HC showed lower FA in the left uncinate fasciculus, the left inferior occipitofrontal fasciculus, and the genu of corpus callosum.
Le Ber et al. (2008)	Structural MRI	Cross-sectional	21 symptomatic <i>GRN</i> (10 fvFTD, 2 fvFTD+PPA, 4 PPA, 2 CBDS, 2 AD, 1 LBD/fvFTD)	20/21 symptomatic <i>GRN</i> showed frontal and/or temporal atrophy, 10/21 parietal and/or occipital atrophy, 16/21 left-right asymmetry.
	SPECT	Cross-sectional	10 symptomatic <i>GRN</i> (6 fvFTD, 1 PPA, 2 CBS, 1 AD), 31 sporadic fvFTD, 28 HC	Symptomatic <i>GRN</i> compared to HC showed hypoperfusion bilaterally in the fronto-cingular, the right posterior temporal cortex, including hippocampus, and the inferior parietal cortex. Compared to sporadic fvFTD, hypoperfusion was seen in the dorsolateral right frontal cortex, the right posterior temporal and inferior parietal cortices, the right hippocampus and the posterior cingulate cortex bilaterally.
Whitwell et al. (2007a)	Structural MRI	Cross-sectional	8 <i>GRN</i> -FTLD (6 bvFTD, 1 svPPA, 1 CBS), 8 sporadic FTLD-U (6 bvFTD, 1 svPPA, 1 CBS), 16 HC	<i>GRN</i> -FTLD compared to HC showed gray matter loss predominantly in the frontal, temporal, and parietal lobes. Compared to sporadic group, gray matter loss was pronounced in the frontal and parietal lobes.

FTLD, frontotemporal lobar degeneration; FTLD-U, FTLD with ubiquitin-positive inclusions; FTD, frontotemporal dementia; bvFTD, behavioral variant FTD; PPA, primary progressive aphasia; svPPA, semantic variant of PPA; nvfPPA, nonfluent variant PPA; fvFTD, frontal variant FTD; CBS, corticobasal syndrome; CBD, corticobasal degeneration; LBD, Lewy body dementia; ALS, amyotrophic lateral sclerosis; MND, motor neurone disease; PSP, progressive supranuclear palsy; MCI, mild cognitive impairment; CSND, clinically symptomatic no dementia; HC, healthy control; SN, salience network; DMN, default mode network; FPN, frontoparietal network; EN, executive network; WMH, white matter hyperintensity; FA, fractional anisotropy; MD, mean diffusivity; AXD, axial diffusivity; ReHo, regional homogeneity; ALFF, amplitude of low frequency fluctuations; fALFF, fractional ALFF; DC, degree centrality; VMHC, voxel-mirrored homotopic connectivity