TMEM106B polymorphism is associated with lower cortical volumes in a clinically diagnosed FTD cohort

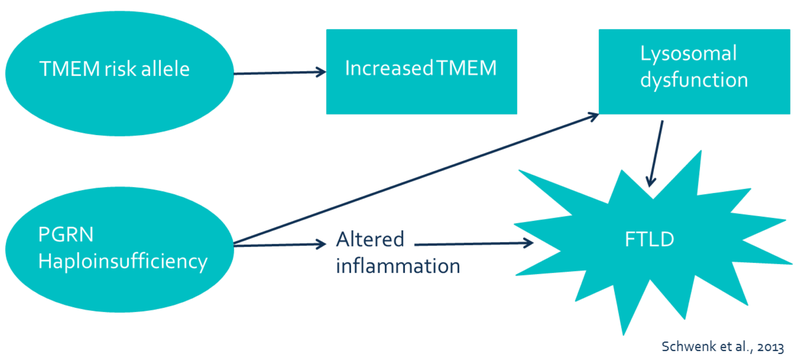
Sophie R Harding[1], Martina Bocchetta[1], Elizabeth Gordon[1], Dave M. Cash[1,2], M. Jorge Cardoso[1,2], Sebastien Ourselin[1,2], Jason D. Warren[1], Simon Mead[3], Jonathan D. Rohrer[1]

1 Dementia Research Centre, and 3 MRC Prion Unit, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
2 Translational Imaging Group, Centre for Medical Image Computing (CMIC), University College London, UK

Background

Frontotemporal dementia (FTD) is a clinically heterogeneous neurodegenerative disease associated with impairment of behaviour, language and motor function. Recently, the TMEM106B rs1990622 A/G polymorphism has been shown to modify the risk of developing FTD, with the risk highest in those homozygous for the A allele. In the normal population, the TMEM106B polymorphism has been shown to be associated with lower cortical volumes in a clinically diagnosed FTD cohort. This study looked at the effects of this polymorphism in FTD.

TMEM106B



TMEM106B is a glycoprotein known to be involved in lysosome function and dendrite maintenance.

Methods

Data was analysed from 200 patients with FTD disorders who had been genotyped and also had available MRI scans. Individuals were divided into two groups: those homozygous for the risk allele (AA), and those with either AG or GG alleles. Statistical analysis showed that the two groups did not differ in *disease duration* (mean (standard deviation), AA: 4.4 (2.5), AG/GG: 4.6 (3.46), *age at scan* (AA: 62.8 (7.5), AG/GG: 62.7 (9.2)) or *age at onset* (AA: 58.4 (8.0), AG/GG:58.2 (9.0))

		bvFTD	CBS	FTD-MND	PNFA	SD	PSP	IBMPFD	Total
Group	**AG/GG**	56	5	4	30	25	1	0	121
	AA	31	2	1	19	21	3	2	79
	Total	87	7	5	49	46	4	2	200

Table 1. Participant Demographics

Once all MRI scans were collected, automated segmentations (GIF Parcellation: Cardoso et al., 2015) were performed following the Neuromorphometrics protocl on volumetric T1-weighted MRI scans to extract cortical regions of interest and total intracranial volume (TIV). Following QC of all GIF segmentations, cortical volumes were compared between groups (after correcting for TIV) in the: Frontal lobe, Temporal lobe, Parietal lobe, Occipital lobe, Cingulate and Insula.

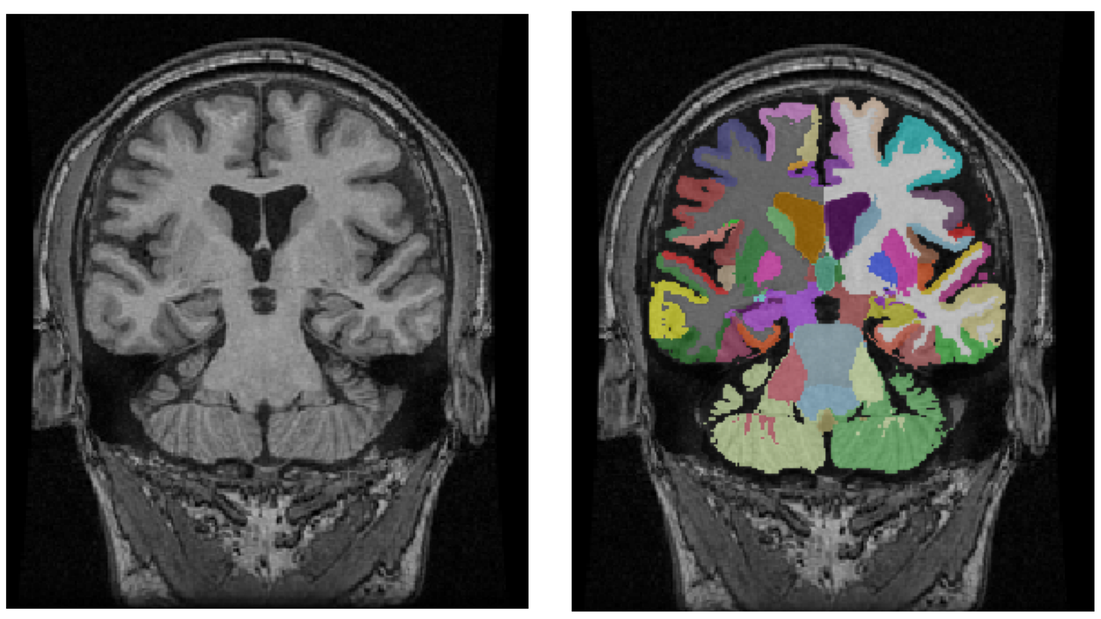


Figure 1.
Left image: bias corrected T1 scan.
Right Image: GIF segmentation overlay over bias corrected T1 scan.

Results

Whole brain analysis

Having combined the two hemispheric volumes together, differences in the mean and SD were computed comparing lobar volumes between the AG/GG carriers and AA (risk allele) carriers (table 2). A Mann-Whitney U test revealed that significantly lower volumes were present in the frontal cortices [AG/GG: 9.6 (1.0) % of TIV, AA: 9.3 (1.0) (p= 0.038)] and cingulate [AG/GG: 1.49 (0.38) % of TIV, AA: 1.44 (0.14) (p= 0.048)]. Additionally a trend was shown in the insula [AG/GG: 0.73 (0.11), AA: 0.70 (0.12) (p= 0.069)].

		Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe	Cingulate	Insula
AA	**Mean**	9.3	6.1	5.5	4.4	1.45	0.70
	SD	1.0	0.9	0.4	0.4	0.14	0.12
AG/GG	**Mean**	9.6	6.3	5.4	4.4	1.49	0.73
	SD	1.0	0.8	0.6	0.4	0.14	0.11

Table 2. Mean and SD of volume % of TIV for each lobe, across the two groups

Post-hoc analysis

Further analysis of interhemispheric lobar volumes revealed that the lower volumes observed across the whole brain, were driven by decreased volumes in the left hemisphere (table 3), rather than the right. This finding is consistent with previous papers that show that in the normal population, individuals with the TMEM106B risk allele have lower lobar volumes in the left hemisphere.

A Mann-Whitney U test revealed that in the left hemisphere only, significantly lower volumes were present in the frontal cortices [AG/GG: 4.8 (0.5) % of TIV, AA: 4.6 (0.1) (p= 0.017)], cingulate [AG/GG: 0.72 (0.08) % of TIV, AA: 0.69 (0.09) (p= 0.017)] and insula [AG/GG: 0.36 (0.06), AA: 0.34 (0.06) (p= 0.018)].

		Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe	Cingulate	Insula
AA	**Mean**	4.6	2.9	2.7	2.2	0.69	0.34
	SD	0.5	0.5	0.3	0.2	0.09	0.06
AG/GG	**Mean**	4.8	3.0	2.7	2.2	0.72	0.36
	SD	0.5	0.5	0.3	0.2	0.08	0.06

Table 3. Mean and SD of volume % of TIV for each lobe, in the left hemisphere.

CONCLUSION

These findings suggest that the TMEM106B risk allele is associated with decreased brain volumes in key areas of the brain that are implicated in FTD. More specifically, this difference in brain volume is dominated by decreased volume of key structures in the left hemisphere.

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