Concordance analysis of atrophy and local gene expression implicates astrocytes in FTD

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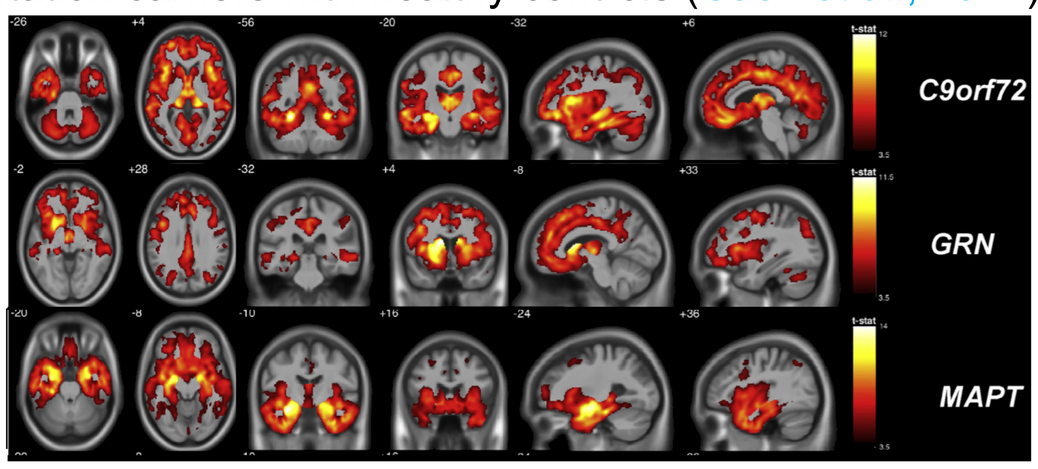
Background

Mutations in three genes are implicated as the major causes of the genetic form of **frontotemporal dementia** (**FTD**): *C9orf72*, *MAPT* and *GRN*. *C9orf72* is also the most common cause of familial amyotrophic lateral sclerosis (ALS). It is unclear whether there are common molecular processes across the genetic forms of FTD. Here we used gene expression data obtained by the **Allen Institute for Brain Sciences (AIBS)** in order to investigate the link between gene expression and prototypical atrophy patterns in mutation carriers.

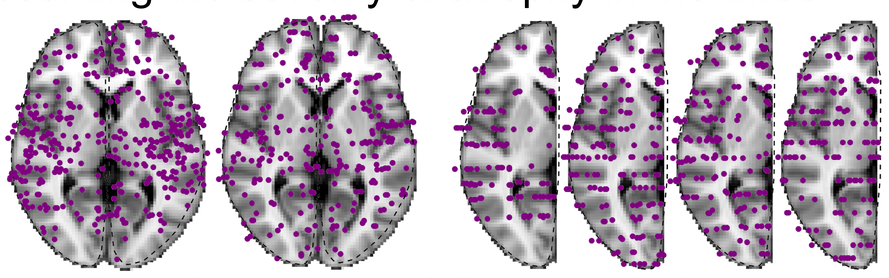
Methods

Atrophy maps: T-score maps from a voxel-based morphometry (VBM) analysis comparing symptomatic mutation carriers with healthy controls (Cash et al., 2017).



Gene Expression: N=1,654 cortical samples from the AIBS **(6 post-mortem donors)**. Each sample comprised 58,692 gene expression probes. After quality control **37,031 probes** were retained, uniquely mapping to one of **16,912 genes**.

Spatial mapping: We used the MNI-coordinates of the 1,654 samples to map each gene expression sample to the t-scores representing the severity of atrophy in the three gene groups.



Statistics: For each probe we tested the association between local gene expression and local atrophy using a linear mixed effects model with donor as random effect:

$$y_{ij} = \beta_0 + t_i\beta_1 + b_{0j} + \varepsilon_{ij}$$

Where, y_{ij} represents the gene expression in brain from donor j at MNI-location i, t_i is the t-value of the group VBM analysis at the same location, b_{0j} is the subject specific offset. We tested for the significance of β_1. P-values were corrected using the method by Holm.

Gene List Interpretation: Overrepresentation test for **Gene Ontology** terms, different **brain cell types marker genes**. Enrichment p-values were FDR-corrected.

Heritability Enrichment: We tested for heritability enrichment in sporadic FTD in brain cell type marker genes and regions known to influence gene expression in monocytes using **LD Score regression** on **GWAS summary statistics** from recent **FTD** and **ALS** GWAS.

Results

Significant genes:

	positive	negative
C9ORF72	1,722	1,927
GRN	1,190	681
MAPT	4,168	5,339
Overlap	452	242

Cell types: Out of 162 marker gene lists for brain cell types 85 were positively significant (higher expression ~ more atrophy) in at least one FTD gene, 28 for all three genes, 10 of which were marking **astrocytes** (of 13 astrocyte marker lists tested!).

Only 25 marker lists were negatively significant in at least one FTD gene; only 2 for all three genes: a generic list for neurons (1.5 fold; Cahoy et al., 2008) and S1 pyramidal neurons (RNA-seq; Zeisel et al., 2015).

Heritability enrichment: Astrocytes can turn neurotoxic following activation my microglia. We found heritability of sporadic FTD and ALS enriched in resting monocytes (p_{FTD}=0.014; p_{ALS}=0.013) and activated monocytes in ALS (p_{IFN}=0.009; p_{LPS}=0.0015).

Conclusions

- **Atrophy** in genetic FTD **co-localizes** with higher expression of **astroctyte marker genes**
- Suggesting higher **astrocyte density** in regions with atrophy
- Severity of astrocytosis and astrocytic apoptosis with both the degree of neuronal loss and the stage of disease (Broe et al., 2004).
- Astrocytes can turn neurotoxic following activation by activated microglia (Liddelow et al., 2017)
- Sporadic forms of FTD and ALS showed significantly enriched heritability in regions known to alter gene expression in resting and activated monocytes
- Astrocytes may have a more active role in FTD

1. Broe, M., Kril, J., & Halliday, G. M. (2004). Astrocytic degeneration relates to the severity of disease in frontotemporal dementia. *Brain : a Journal of Neurology*, *127*(Pt 10), 2214–2220. http://doi.org/10.1093/brain/awh250
2. Cash, D. M., et al. (2017). Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. *Neurobiology of Aging*, *62*, 191–196. http://doi.org/10.1016/j.neurobiolaging.2017.10.008
3. Cahoy, J. D., et al. (2008). A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience*, *28*(1), 264–278. http://doi.org/10.1523/JNEUROSCI.4178-07.2008
4. Liddelow, S. A., et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, *541*(7638), 481–487. http://doi.org/10.1038/nature21029
5. Zeisel, A., et al. (2015). Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. *Science (New York, NY)*, *347*(6226), 1138–1142. http://doi.org/10.1126/science.aaa1934

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