P3-271

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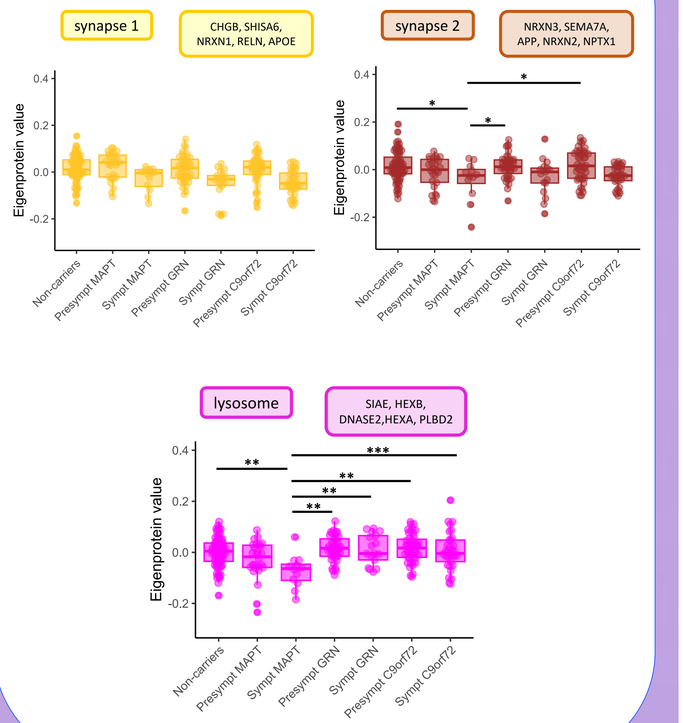
Specific decrease of lysosomal-related proteins in symptomatic *MAPT* mutation carriers and decrease of synaptic related proteins across the genetic FTD spectrum.



Confirmed by individual candidates from a broad proteomics dataset in the GENFI study.

Targeted proteomic search reveals new actors in the synaptic and lysosomal dysfunction in genetic FTD, a GENFI study.

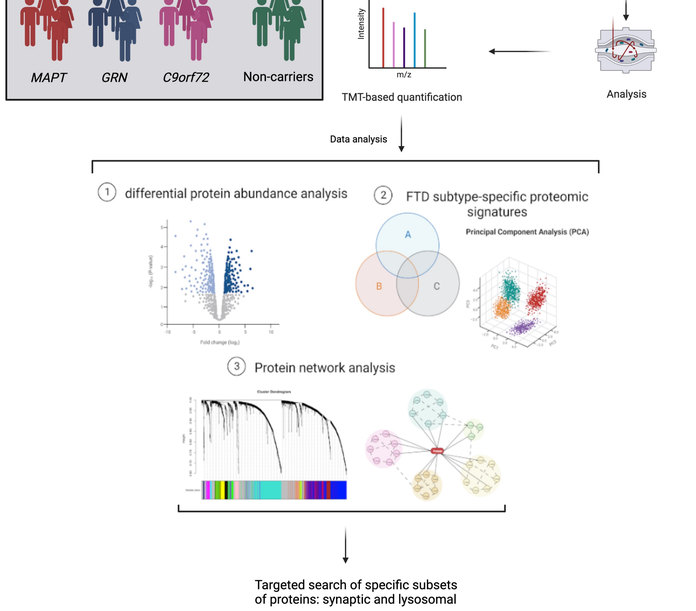
Sophia Weiner*, Frederika Malichova*, Joel Simrén , Mathias Sauer, Imogen Swift, Carolin Heller, Kathryn Knowles, GENFI consortium, Kaj Blennow, Henrik Zetterberg, Jonathan Rohrer, Johan Gobom*, **Aitana Sogorb-Esteve***.

BACKGROUND

- There are limited fluid biomarkers to understand the underlying mechanisms of the frontotemporal (FTD) spectrum.
- Studying fluid biomarkers in genetics forms (approx. a third of FTD) provides greater insight in the relationship with pathologies.
- Synaptic and lysosomal dysfunction appear to be common features across the FTD spectrum.

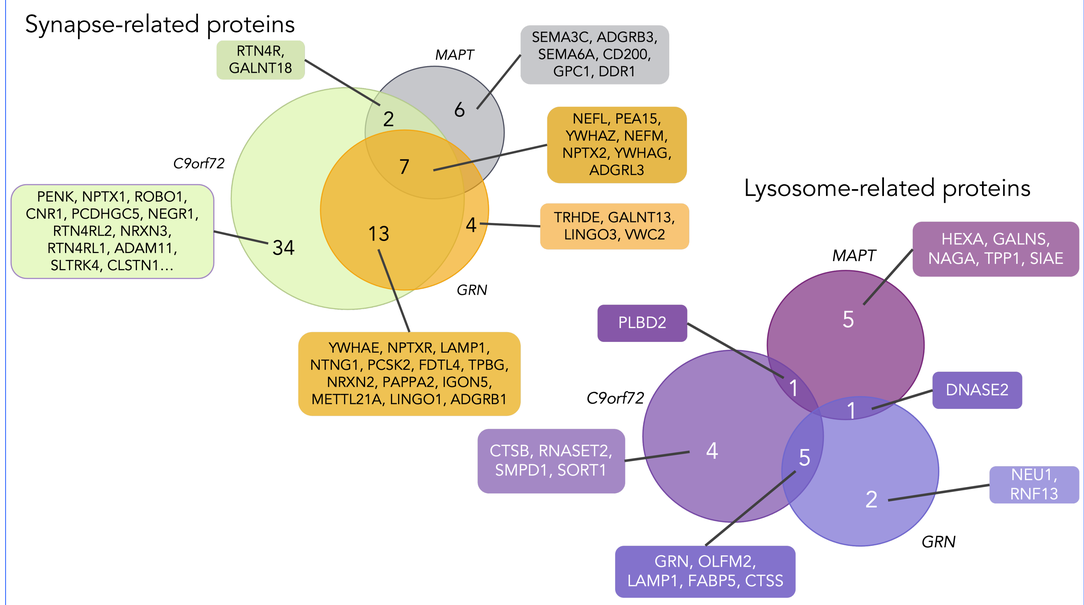
METHODS

We performed a targeted search for synapse- and lysosome-related proteins in a Tandem Mass Tag (TMT) dataset obtained from 248 cerebrospinal samples from the GENFI cohort. The workflow is shown in the figure below.

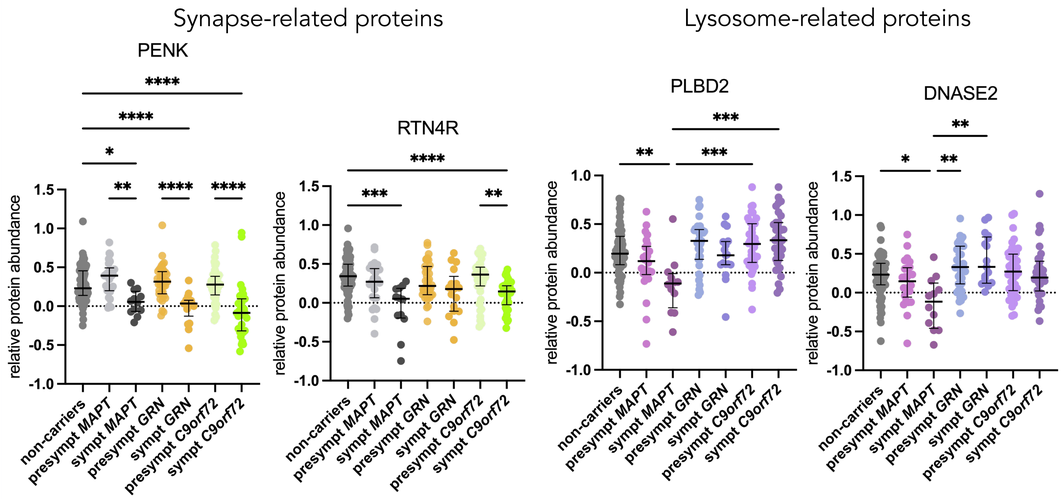


RESULTS

Two modules with synapse-related proteins show a trend to decrease in symptomatic mutation carriers from the three groups. The module containing lysosome-related proteins is specifically decreased in symptomatic *MAPT* mutation carriers.



In the Venn diagrams we have included the proteins which were statistically significant in comparison of the symptomatic group versus non-carriers. Only 7 synapse-related proteins and none lysosome-related proteins overlapped across all genetic groups.



When looking at individual proteins we saw the same patterns as in the broad study.

CONCLUSION

This study shows evidence of alterations of synapse- and lysosome-related proteins in genetic FTD which implies a novel insight from the existing literature.

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