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Exploring the utility of synaptic markers in frontotemporal dementia

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WHY?

Approximately a third of frontotemporal dementia (FTD) is genetic with mutations in three genes accounting for the majority of the inheritance: C9orf72, GRN and MAPT. Synaptic dysfunction is a common mechanism in all of them and the use of fluid biomarkers could be helpful to improve the diagnostic accuracy and useful as a readout of cellular dysfunction within therapeutic trials.

HOW?

We aim to study changes in synaptic markers in the GENetic Frontotemporal dementia Initiative (GENFI) cohort. GENFI is formed by presymptomatic and symptomatic participants who carry one of the three mutations accounting for FTD and by non-mutation carriers as controls.

Using a LC PRM-MS set-up we target 15 synaptic proteins (Figure 1) in cerebrospinal fluid (CSF) samples from the GENFI cohort.

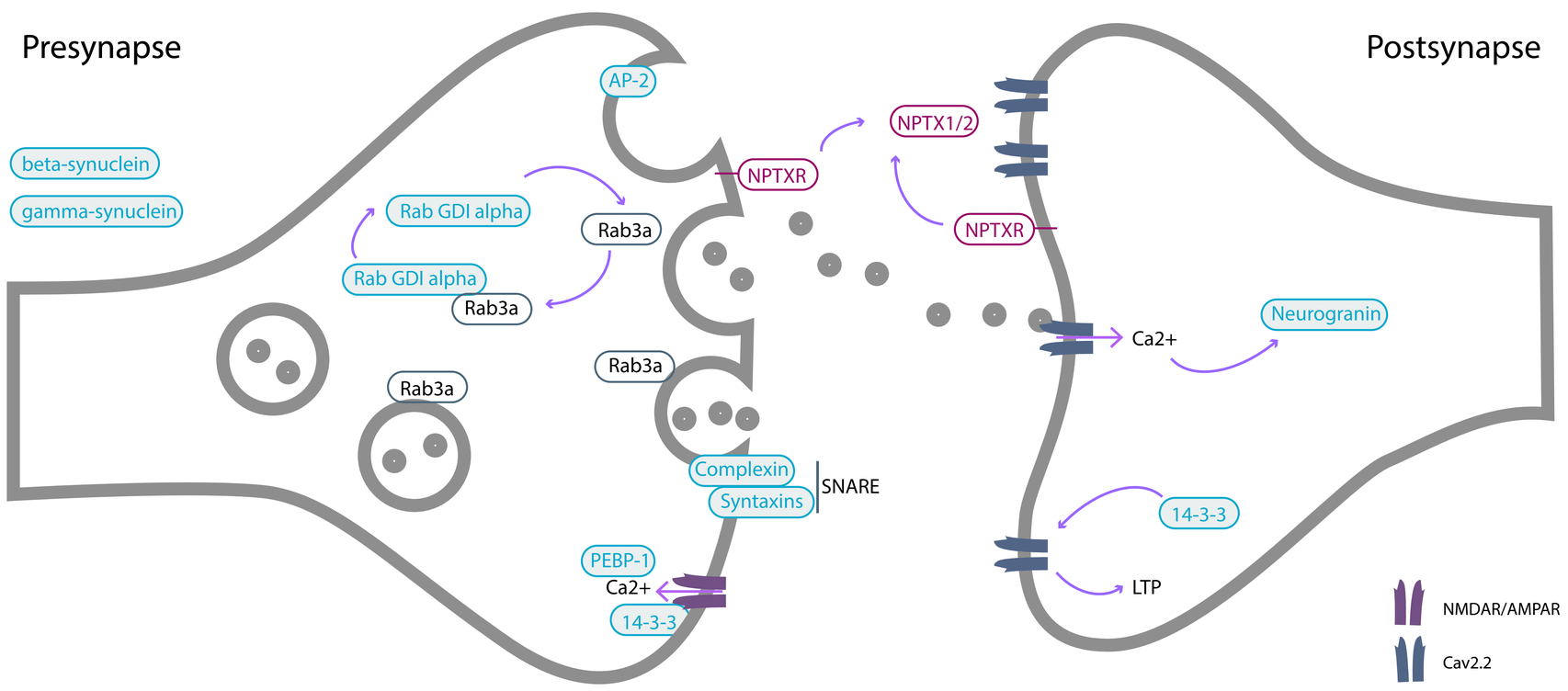

***Figure 1**. Diagrammatic representation of the synapse and the role of the different synaptic proteins included within the mass spectrometry panel.*

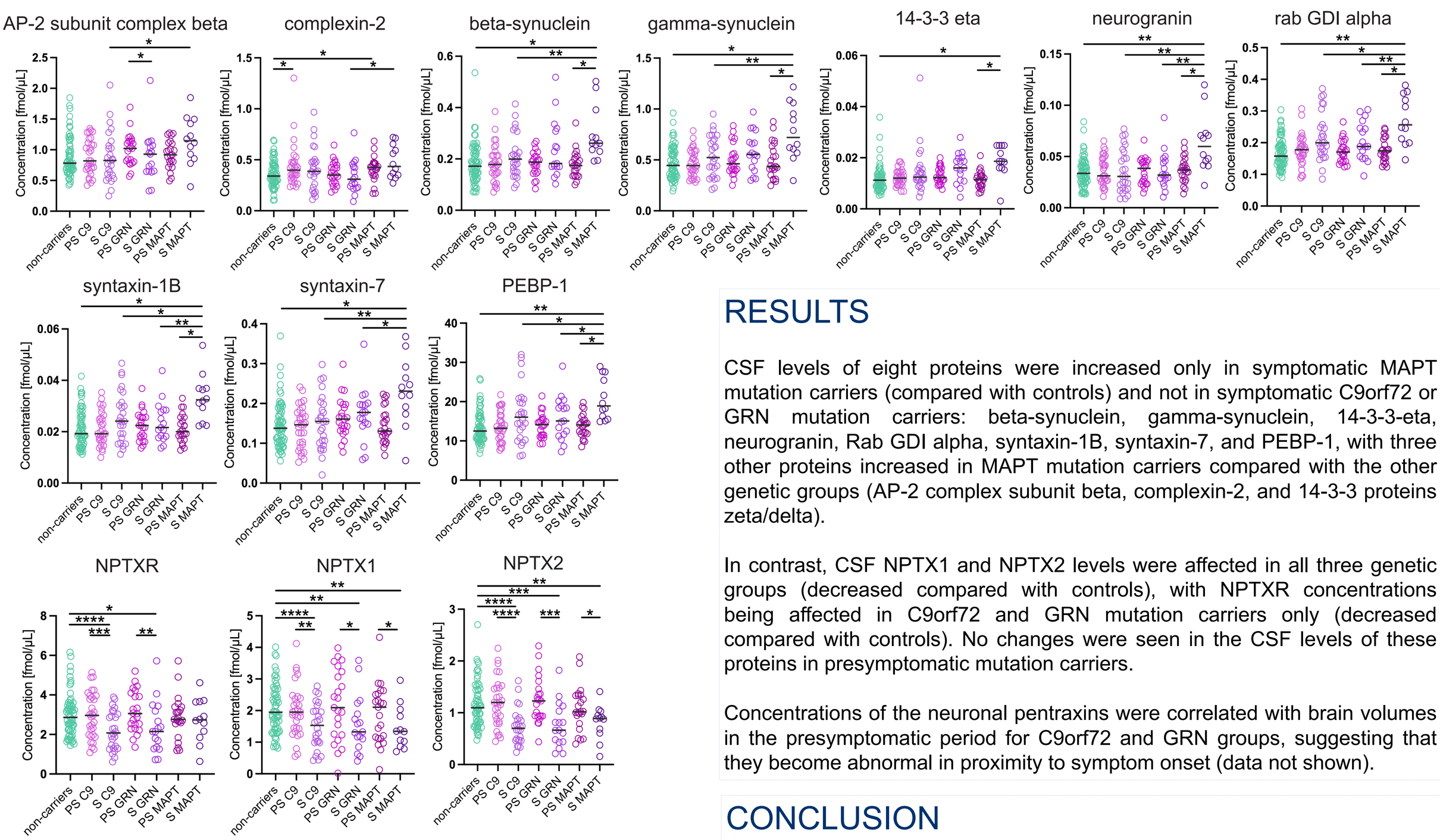

***Figure 2**. CSF concentrations of the synaptic panel proteins in the GENFI cohort including 23 presymptomatic* MAPT *(PS MAPT), 31* C9orf72 *(PS C9) and 23* GRN *(PS GRN) mutation carriers, 12 symptomatic MAPT (S MAPT), 26* C9orf72 *(S C9) and 17* GRN *(S GRN) mutation carriers, and 61 non-carriers. Linear regression model adjusting for age at CSF sample collection and sex; bootstrapping with 2000 repetitions was used if the synaptic measures were not normally distributed. Results shown in fmol/µL. p-values: * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001, and **** p ≤ 0.0001. The bars indicate the median.*

RESULTS

CSF levels of eight proteins were increased only in symptomatic MAPT mutation carriers (compared with controls) and not in symptomatic C9orf72 or GRN mutation carriers: beta-synuclein, gamma-synuclein, 14-3-3-eta, neurogranin, Rab GDI alpha, syntaxin-1B, syntaxin-7, and PEBP-1, with three other proteins increased in MAPT mutation carriers compared with the other genetic groups (AP-2 complex subunit beta, complexin-2, and 14-3-3 proteins zeta/delta).

In contrast, CSF NPTX1 and NPTX2 levels were affected in all three genetic groups (decreased compared with controls), with NPTXR concentrations being affected in C9orf72 and GRN mutation carriers only (decreased compared with controls). No changes were seen in the CSF levels of these proteins in presymptomatic mutation carriers.

Concentrations of the neuronal pentraxins were correlated with brain volumes in the presymptomatic period for C9orf72 and GRN groups, suggesting that they become abnormal in proximity to symptom onset (data not shown).

CONCLUSION

Differential synaptic impairment is seen in the genetic forms of FTD, with abnormalities in multiple measures in those with MAPT mutations, but only changes in neuronal pentraxins within the GRN and C9orf72 mutation groups. Such markers may be useful in future trials as measures of synaptic dysfunction, but further work is needed to understand how these markers change throughout the course of the disease.

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