Differential synaptic marker involvement in the different genetic forms of frontotemporal dementia

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INTRODUCTION

A third of frontotemporal dementia (FTD) is genetic with mutations in three genes accounting for most 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.

METHODS

In this study we included 193 CSF samples from the GENetic FTD Initiative (GENFI): 77 presymptomatic (31 C9orf72/P5 C9, 23 GRN (P5 GRN), 23 MAPT (P5 MAPT)), 55 symptomatic mutation carriers (26 C9orf72 (sym P9), 17 GRN (sym GRN), 12 MAPT (sym MAPT)) and 61 mutation-negative controls (non-carriers). The methodology used was a microflow LC PRM-MS set-up targeting 15 synaptic proteins: 14-3-3 proteins (eta, zeta/delta and epsilon), AP-2 complex subunit beta, beta-synuclein, gamma-synuclein, complexin-2, neurogranin, neuronal pentraxin receptor (NPTXR), neuronal pentraxin 1 (NPTX1), neuronal pentraxin 2 (NPTX2), phosphatidylethanolamine-binding protein 1 (PEBP1), rabbit GDP dissociation inhibitor alpha (rab GDIα), syntaxin-1B and syntaxin-7. Mutation carrier groups were compared to each other and to controls using a boosted linear regression model, adjusting for age and sex.

CONCLUSION

Here we show a differential involvement of synaptic markers in the genetic forms of FTD. The impairment is seen particularly in those with MAPT mutations, with only the neuronal pentraxins affected in GRN and C9orf72 mutation carriers.

FIGURE. Levels of synaptic markers in CSF from the different genetic groups included in the study. Levels expressed in fmol/mL and p-value of each significant change indicated in each graph.

Eight proteins were increased only in symptomatic MAPT mutation carriers (compared with controls) and not in symptomatic C9orf72 or GRN mutation carriers: 14-3-3-eta, beta-synuclein, gamma-synuclein, neurogranin, PEBP1., rab GDIα, syntaxin-1B and syntaxin-7. In contrast, NPTX1 and NPTX2 were affected in all three genetic groups (decreased compared to controls), with NPTXR being affected in C9orf72 and GRN mutation carriers only (decreased compared to controls). No changes were seen in presymptomatic mutation carriers in these proteins.