Imogen Swift

Prosaposin: a lysosomal CSF biomarker of progranulin-associated frontotemporal dementia

State of the art

Heterozygous mutations in the progranulin gene (GRN) are a key cause of frontotemporal dementia (FTD), representing around 5-10% of all cases. These pathogenic mutations lead to significantly lower biofluid concentrations of the progranulin protein (PGRN). However, we currently lack a complete understanding of the underlying biology of GRN-related FTD as well as biomarkers that will help to determine treatment efficacy. In this study we aimed to quantify biofluid levels for the prosaposin (PSAP) protein, which is a known binding partner of PGRN and important for PGRN's biological function.

Methodology

Using a novel MSD-based assay, CSF PSAP concentration was measured in 178 individuals from the GENFI study, including 55 C9orf72 mutation carriers (36 presymptomatic and 19 symptomatic), 42 GRNmutation carriers (32 presymptomatic and 10 symptomatic), and 24 MAPT mutation carriers (17 presymptomatic and 7 symptomatic) as well as 56 controls. Plasma PSAP from a pilot cohort of 24 individuals (7 presymptomatic and 5 symptomatic GRN mutation carriers as well as 12 controls) was also tested.

Results

Significantly higher concentrations of CSF PSAP were found in both presymptomatic and symptomatic GRNmutation carriers compared to controls ($p=0.0207$ and $p=0.0012$, respectively). However, no significant differences in plasma PSAP concentration were observed between either presymptomatic or symptomatic GRN carriers and controls ($p=0.4434$ and $p=0.9779$, respectively).

Conclusion

These findings suggest that CSF PSAP concentration could be a valuable biomarker for use in upcoming trials as well as play an important role in further understanding the molecular basis of GRN-related FTD.

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