Specific biomarkers for C9orf72 FTD/ALS could expedite the journey towards effective therapies

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A hexanucleotide repeat expansion in the C9orf72 gene is a common genetic cause of ALS and FTD. The repeats are translated into five different dipeptide repeat proteins (DPRs). In this issue, Lehmer et al (2017) demonstrate that one of these DPRs, poly(GP), can be measured in the CSF of individuals with C9orf72 mutations. In conjunction with the findings from another recent study (Gendron et al, 2017), these DPR biomarkers may prove to be extremely valuable in the quest for effective therapies for C9FTD/ALS.

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FTLD-specific Clinical Dementia Rating, or an association with an ALS or FTD phenotype, age of disease onset, or survival. This stability of poly(GP) levels may enhance its value as a pharmacodynamic biomarker. In a clinical trial, for each patient, relative pre- and post-intervention values would be compared; therefore, a stable marker showing normalisation with a therapy is ideal. As an elegant proof of principle of this concept, Gendron et al (2017) show that treating C9orf72 iPSC-derived neurons and a C9orf72 mouse model with ASOs reduces poly(GP) levels. The levels of intracellular poly(GP) in C9orf72 iPSC neurons correlates with extracellular levels in media bathing the cells, and in a mouse model, CSF poly(GP) correlates with poly(GP) in brain homogenates. This indicates that CSF poly(GP) levels are likely to reflect intraneuronal levels in the CNS. However, it is important to note that in their longitudinal analysis of a small patient cohort, in some individuals CSF poly(GP) naturally decreases over time, which should be accounted for in clinical trials. An emerging theme from trials in Alzheimer’s disease (AD) is that administering treatment early in the disease course, before extensive neurodegeneration, may be most effective; therefore, detection of CSF poly(GP) in asymptomatic individuals may have great value for implementing early treatment. Lehmer et al (2017) show that CSF levels of neurofilaments (NfL and pNFH), markers of axonal damage, are raised in symptomatic but not asymptomatic C9orf72 mutation carriers, in agreement with recent studies of neurofilaments as ALS diagnostic and prognostic biomarkers (Fig 1). The combination of both biomarkers could provide evidence of target engagement and functional rescue.

Lehmer et al (2017) suggest CSF poly(GP) could be used alongside genotyping as a diagnostic biomarker, and were able to reclassify one patient misdiagnosed with AD as C9FTD. Due to somatic instability of GGGGCC repeats, it is possible that patients without an expansion in blood DNA have expansions in the CNS; therefore, the addition of CSF poly(GP) could add diagnostic value. However, it is important to note that both studies describe a small number of false positives, non-C9orf72 individuals with elevated poly(GP), or false negatives, C9orf72 individuals with non-detectable poly(GP). Improving the sensitivity and specificity of these assays is critical and may require the use of other potentially more sensitive platforms, such as the Simoa (single molecule array), which was used on a subset of samples by Gendron et al (2017). Lehmer et al (2017) use monoclonal antibodies in their immunoassay, which are less variable and can be produced at higher throughput than polyclonal antibodies, so may provide an additional advantage. Developing similar assays for other more toxic DPRs may also be beneficial, as they may correlate better with progression or prognosis.

In addition to CSF, Gendron et al (2017) specifically detected poly(GP) in peripheral blood mononuclear cells. Detection in blood would be advantageous for repeat measurements in clinical trials. This could mark a significant step forward, but further studies are needed to determine whether blood and CSF poly(GP) levels correlate.

In conclusion, developing promising biomarkers should be integral to clinical trials in C9FTD/ALS, and a biomarker assay should ideally be sensitive, specific, reproducible with low variability, standardised and affordable. These studies now highlight CSF poly(GP) as one such potential candidate.

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References


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