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COMMENTARY

C9orf72 immunohistochemistry in Alzheimer's disease

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See related research by Satoh *et al.*, http://alzres.com/content/4/4/33

Abstract

Mutation in chromosome 9 open reading frame 72 (*C9orf72*) is a major genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), referred to as C9FTD/ALS. The function of the protein is currently unknown, and the pathomechanism of C9FTD/ALS remains to be elucidated. The study by Satoh and colleagues in the previous issue of *Alzheimer's Research & Therapy* presents important new findings on C9orf72 protein expression in neurodegenerative disorders along with characterization of C9orf72 antibodies.

Chromosome 9 open reading frame 72 (C9orf72) is a protein with unknown function and a high level of expression in the brain and spinal cord. The discovery of expanded heptanucleotide repeat mutations as the most common genetic cause of familial and sporadic frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) [1,2] provided further evidence for a phenotypic spectrum with overlapping genetic [3-5], pathological [6,7], and clinical [8,9] features. *C9orf72* mutant FTD and ALS (C9FTD/ALS) cases reveal a characteristic neuropathological signature with abundant p62-positive inclusions in the hippocampus and cerebellum [6,7] and a unique pattern of ubiquilin pathology [10]. *C9orf72* repeat expansion mutation in large cohorts of patients with AD has been either absent [11] or identified exceedingly rarely [12].

In the previous issue of *Alzheimer's Research & Therapy*, Satoh and colleagues [13] present an analysis of C9orf72 expression and its relation to ubiquitin, p62, and ubiquilin-1, ubiquilin-2 immunoreactivity in control, Alzheimer's disease (AD), sporadic ALS, Parkinson's disease, and multiple system atrophy brains. Early studies have consistently shown that C9orf72 is negative in intracellular inclusions including tau-positive structures except for Pick bodies (for references, see [13]). In contrast to these previous studies, Satoh and colleagues report C9orf72 in a subset of dystrophic neurites in AD. Another major finding is the demonstration of C9orf72 and ubiquilin-1 positivity in a cluster of dystrophic neurites in senile plaques in AD brains by using antibodies discriminating ubiquilin-1 from ubiquilin-2; these results warrant further studies into the role of ubiquilin in neurodegeneration. The thorough analysis of two different anti-C9orf72 antibodies for the pattern of immunoreactivity, specificity, cross-reactivities is an important aspect of the study. The results suggest that the testing of further antibodies available on the market and the generation of novel highly specific anti-C9orf72 antibodies are necessary to facilitate research into neurodegenerative diseases, in particular C9FTD/ALS. Unfortunately, *C9orf72* mutation status has not been analyzed in the included cases either; Satoh and colleagues assume that cases are likely to be negative in view of the low prevalence of *C9orf72* mutation in ALS and FTD in Japanese patients [14] in comparison with Caucasian patients [15]. Pathological proteins incorporated into characteristic inclusions in neurodegenerative diseases are rather detergent-insoluble; the analysis of this key feature is still awaited. The case numbers are low in this study. Therefore, as the authors themselves have suggested, further studies are needed to test the presented findings in larger cohorts and by more detailed analysis. This paper provides a nidus around which the presented observations can be more robustly studied and clarified.

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Abbreviations

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; C9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; C9orf72, chromosome 9 open reading frame 72; FTD, frontotemporal dementia.

Competing interests

The author declares that he has no competing interests.

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