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Impaired ribosome-associated quality control of *C9orf72*-associated arginine-rich dipeptide-repeat proteins

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Defects in ribosome-associated quality control and its associated factors have been implicated in the accumulation of aberrant proteins and neurodegeneration. The *C9orf72* repeat expansion mutation is the most prevalent pathogenic genetic variant of amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration (FTD). *C9orf72* repeat-associated non-AUG (RAN) translation has been suggested to involve inefficient translation elongation, lead to ribosomal pausing and activation of ribosome-associated quality control (RQC) pathways. However, the role of the RQC complex in the processing of proteins generated through this non-canonical translation is not well understood.
We utilized reporter constructs containing the *C9orf72*-associated hexanucleotide repeats, RQC complex deficient cell models and stained *C9orf72*-expansion carrier brain tissue for RQC-associated markers to understand its role in dipeptide repeat protein (DPR) pathology.
Using translational stalling reporter constructs, we showed that the hexanucleotide repeat associated with the *C9orf72*-expansion induces ribosome stalling when arginine (R)-rich proteins are synthesized in a length-dependent manner. However, despite inducing ribosome stalling which triggers RQC complex recruitment, these R-rich proteins are not efficiently processed by the core components of the RQC complex (listerin, nuclear export mediator factor (NEMF) and valosin containing protein (VCP)) in cells. Deficient processing by this complex may be implicated in *C9orf72*-expansion associated disease as DPR inclusions were observed to be predominantly devoid of ubiquitin and co-localize with NEMF in patient brain tissue.
These findings suggest that impaired processing of these R-rich proteins derived from *C9orf72* RAN translation by the RQC complex may contribute to protein homeostasis dysregulation observed in *C9orf72*-expansion associated ALS and FTD.

Conflicts of interest

N/A