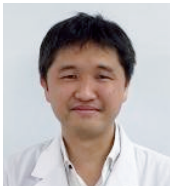
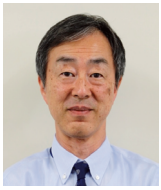
Healthcare, Drug discovery

# Elucidation of the mechanism of abnormally expanded repeat RNA accumulation and development of novel therapeutic strategies thereof in frontotemporal dementia

Department of Psychiatry, Graduate School of Medicine
Assistant Professor Kohji Mori
Researchmap https://researchmap.jp/kmori_psy/?lang=en
Professor Manabu Ikeda
Researchmap https://researchmap.jp/manabu_ikeda?lang=en





## Abstract

Frontotemporal dementia (FTD) is a neurocognitive disorder with prominent neurodegeneration in the frontal and temporal lobes, resulting in behavioral abnormalities, personality changes, and aphasia, and is a frequent cause of early-onset dementia. Aberrantly expanded repeats in the introns of the *C9orf72* (chromosome 9 open reading frame 72) gene cause two intractable diseases: frontotemporal dementia (also called frontotemporal lobar degeneration) and amyotrophic lateral sclerosis (ALS). In this study, we revealed that expanded repeat RNAs derived from the mutated *C9orf72* gene are degraded by an RNA-degrading enzyme complex called the RNA exosome. In addition, we showed that repeat proteins, that are produced (translated) from the repeat RNA by a non-canonical mechanism, suppresses the activity of the RNA exosome and accelerates the accumulation of the pathogenic repeat RNA.

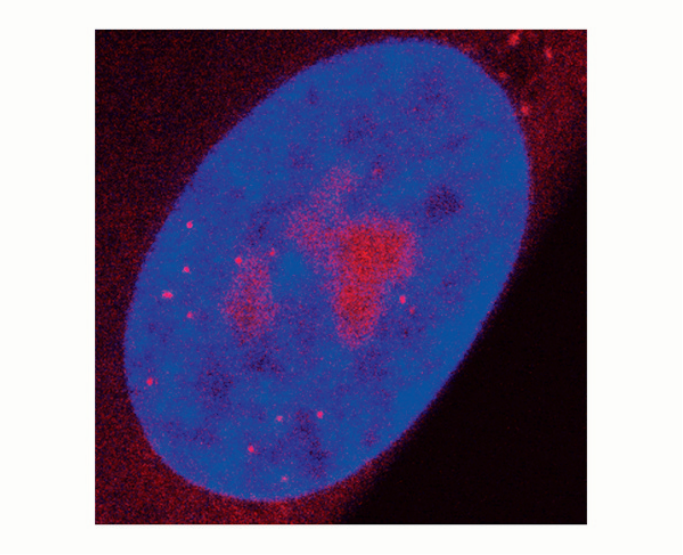
## Background & Results

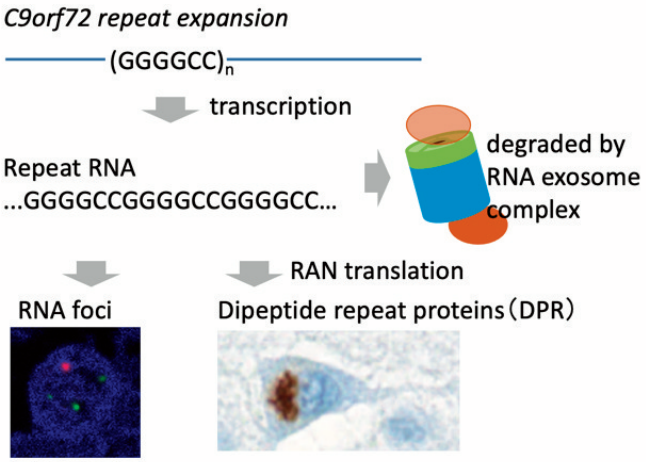
So far, no treatments can cure FTD/ALS, or even slow its progression. The expanded tandem DNA repeats are transcribed into repeat RNA, which often forms RNA aggregates in the cell (Figure 1). In addition, we have previously shown that the *C9orf72* repeat RNA undergoes atypical translation to produce repeat proteins that abundantly accumulate in neurons. Repeat RNA can be toxic itself and is the source of highly toxic repeat protein.

Although it was known that aberrantly elongated repeat RNAs accumulated in patient derived *C9orf72* mutant cells, it was not clear by what mechanism the repeat RNAs were degraded or escaped degradation and accumulated in the cells. Using disease model cells, we revealed that the repeat RNA is degraded intracellularly by RNA exosomes. Furthermore, we found that the arginine containing repeat protein, which is produced by repeat associated non-AUG translation (RAN translation) of the repeat RNA, inhibits the activity of RNA exosomes and thus suppresses the degradation of the aberrant repeat RNA, resulting in the accumulation of more aberrant repeat RNA in the cell.

## Significance of the research and Future perspective

Our findings provide potential avenues to explore for therapy options. The intracellular accumulation of repeat RNA due to abnormal RNA degradation would leads to increased production of highly toxic repeat proteins, which in turn results in neurodegeneration. Since mutations in RNA exosome components cause another neurological disease called pontocerebellar hypoplasia, it is possible that abnormal RNA metabolism due to RNA exosome disruption by repeat proteins itself modifies the pathophysiology of FTD/ALS. Taking these into account, reducing repeat RNA by restoring/augmenting the activity of RNA exosome complex could be a therapeutic option in FTD/ALS caused by this genetic abnormality. Our group aims to develop novel therapies by promoting repeat RNA metabolism or inhibiting its translation into repeat proteins.



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Treatise
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Keyword frontotemporal dementia, frontotemporal lobar degeneration, RNA, RAN translation