

## Editorial

# Intronic *C9orf72* Mutation Expanding on Neurodegenerative Disorders and Other Diseases

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## EDITORIAL

In 2011, *C9orf72* GGGGCC hexanucleotide repeat expansion in intron 1 was reported to be the most common cause of Caucasian sporadic and familial amyotrophic lateral sclerosis (ALS) / frontotemporal dementia (FTD). Indeed, the frequency of the repeat expansion was up to 3%–21% in sporadic ALS and 21%–57% in familial ALS drawing our interest [1-3]. All patients with the repeat expansion had (partly or fully) a founder haplotype, suggesting a one-off expansion occurring about 1500 years ago [3].

The Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS) analyzed 563 (552 sporadic, 11 familial) Japanese patients with ALS and found the repeat expansion in 2/552 = 0.4% of sporadic ALS patients and 0/11 = 0% of familial ALS patients [4]. The sibling of one of the two Japanese probands was found to have primary progressive aphasia (PPA) after detection of the repeat expansion. In this family, the proband with ALS had no dementia or psychosis and the sibling had no motor neuron signs, no positive clinical and laboratory findings including needle electromyogram. Notably, after the detection of the proband with “sporadic” ALS, the existence of quite different (not overlapped) clinical phenotypes of ALS and PPA caused by the same *C9orf72* mutation in the same family were found subsequently.

The combination of other publications reveals that *C9orf72* repeat expansion accounts for 0.4% (4/891) of sporadic ALS, 2.8% (3/109) of familial ALS, and 0% (0/377) of normal healthy controls in Japanese [4-6]. Of note, the Kii peninsula, which has recorded a high incidence of ALS or ALS/PDC (parkinsonism-dementia complex), frequency of the *C9orf72* repeat expansion was 20% (3/15), indicating high prevalence [6]. However, the results from the Kii peninsula revealed that whereas clinical symptoms of patients with the *C9orf72* repeat expansion overlap those of ALS/PDC, ALS patients with the *C9orf72* repeat expansion around Kozagawa area seemed to be different from ALS/PDC patients around Hohara area based on the reported clinical and pathological features. In addition, the *C9orf72* repeat

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expansion was not detected in ALS/PDC of Guam [7]. All the Japanese patients with the repeat expansion had a common risk haplotype within narrower region than Finnish one, suggesting a common founder effect which spread from Europe to East Asia genetically [3-6].

In Japanese patients with FTD, although only a small number of patients have been screened, of the our 75 (48 familial, 27 sporadic) patients with frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), or corticobasal syndrome (CBS) none had *C9orf72* repeat expansion (0/75 = 0%) [8]. Whereas, a very recent paper reported that the *C9orf72* repeat expansion was also observed in parkinsonism, Parkinson's disease, and PSP [9]. Moreover, relations between the *C9orf72* repeat expansion and Alzheimer's disease have been discussed, suggesting genetic heterogeneity of *C9orf72* mutation.

Based on the Caucasian data, no pathogenic mutations in coding exons of *C9orf72* have been detected. Anticipation and severer phenotype depending on the repeat length, which are often observed in polyglutamine diseases caused by triplet repeats (CAG), have not been observed so far. Intronic repeat expansion and heterogeneity in each somatic cell and tissue have been pointed out as the reasons, however, the precise reasons are not well known. “What is an exact cause that determines or separates clinical phenotype of ALS, FTD, and parkinsonism?” are very interesting questions that need to be solved.

Pathologically, ALS patients with the *C9orf72* repeat expansion have TDP-43 positive inclusion in the spinal cord as well as classical ALS. Moreover, p62-positive (in excess of TDP-43) neuronal cytoplasmic inclusions (NCIs) in frontal cortex, hippocampus (CA4), and cerebellum were characteristic features of the ALS patients with the *C9orf72* repeat expansion [10].

Concerning pathogenesis, “how does intronic GGGGCC expansion cause neurodegeneration?” is a very interesting question because this answer would lead to the universal pathogenesis of neurodegeneration by elucidating molecular genetic mechanisms. One potential mechanism was a loss of function based on decreased mRNA levels [1,2,11] and the other

potential mechanism was a toxic RNA gain of function based on the accumulation of RNA transcripts containing the GGGGCC repeat [2]. The latter mechanism suggests the RNA structure of GGGGCC repeats renders these transcripts susceptible to an unconventional mechanism of translation—repeat associated non-ATG (RAN) translation [12]. Antibodies generated against putative GGGGCC repeat RAN translated peptides (anti-C9RANT) detected high molecular weight, insoluble material in brain elucidating homogenates, and neuronal inclusions throughout the central nervous system of ALS/FTD patients with the *C9orf72* repeat expansion specifically [12]. Most of these pathologically characteristic inclusions contain poly- (Gly-Ala) and to a lesser extent poly- (Gly-Pro) and poly- (Gly-Arg) dipeptide-repeat proteins presumably generated by non-ATG-initiated translation from the expanded GGGGCC repeat in three reading frames (GGG-GCC, GGG-CCG, and GGC-CGG) [12,13]. These molecular mechanisms and abnormal accumulations which may cause ALS/FTD are good targets for essential therapies of ALS and FTD.

Thus, studies for *C9orf72* have provided important clues in the search to find the real molecular mechanisms and the essential therapeutic strategies of ALS and FTD. According to the findings of *C9orf72*, ALS and FTD were thought to have common molecular mechanisms and spread on the same disease spectrum. Furthermore, parkinsonism might also be in the same situation. These recent progresses make us rethink the importance of considering genetic testing after checking a detailed family history in neurodegenerative disorders. Based on the Caucasian and Asian data, the *C9orf72* repeat expansion spread while having the common founder effect in sporadic and familial ALS/FTD [4]. Consequently, the family histories of patients with ALS, even sporadic ALS, and other complicated neurological disorders such as dementia and parkinsonism should be examined and genetically tested more actively.

Diagnosis, management, and genetic counseling by longitudinal follow up and penetrance detection of patients with the *C9orf72* repeat expansion is evidence of the progress being made. Further studies about *C9orf72* will clarify the pathogenesis and help reveal the treatment of familial and sporadic neurodegenerative disorders such as ALS, FTD, and parkinsonism.

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## REFERENCES

1. Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011; 72: 257-268.
2. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011; 72: 245-256.
3. Majounie E, Renton AE, Mok K, Doppler EG, Waite A, Rollinson S, et al. Frequency of the *C9orf72* hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol* 2012; 11: 323-330.
4. Ogaki K, Li Y, Atsuta N, Tomiyama H, Funayama M, Watanabe H, et al. Analysis of *C9orf72* repeat expansion in 563 Japanese patients with amyotrophic lateral sclerosis. *Neurobiol Aging* 2012; 33: 2527. e11-16.
5. Konno T, Shiga A, Tsujino A, Sugai A, Kato T, Kanai K, et al. Japanese amyotrophic lateral sclerosis patients with GGGGCC hexanucleotide repeat expansion in *C9ORF72*. *J Neurol Neurosurg Psychiatry* 2013; 84: 398-401.
6. Ishiura H, Takahashi Y, Mitsui J, Yoshida S, Kihira T, Kokubo Y, et al. *C9ORF72* repeat expansion in amyotrophic lateral sclerosis in the Kii peninsula of Japan. *Arch Neurol* 2012; 69: 1154-1158.
7. Dombroski BA, Galasko DR, Mata IF, Zabetian CP, Craig UK, Garruto RM, et al. *C9orf72* hexanucleotide repeat expansion and guam amyotrophic lateral sclerosis-parkinsonism-dementia complex. *JAMA Neurol* 2013; 70: 742-745.
8. Ogaki K, Li Y, Takahashi M, Ishikawa K, Kobayashi T, Nonaka T, et al. Analyses of the *MAPT*, *PGRN*, and *C9orf72* mutations in Japanese patients with FTL, PSP, and CBS. *Parkinsonism Relat Disord* 2013; 19: 15-20.
9. Lesage S, Le Ber I, Condroyer C, Broussolle E, Gabelle A, Thobois S, et al. *C9orf72* repeat expansions are a rare genetic cause of parkinsonism. *Brain* 2013; 136: 385-391.
10. Mahoney CJ, Beck J, Rohrer JD, Lashley T, Mok K, Shakespeare T, et al. Frontotemporal dementia with the *C9ORF72* hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. *Brain* 2012; 135: 736-750.
11. Gijssels I, Van Langenhove T, van der Zee J, Sleegers K, Philtjens S, Kleinberger G, et al. A *C9orf72* promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. *Lancet Neurol* 2012; 11: 54-65.
12. Ash PE, Bieniek KF, Gendron TF, Caulfield T, Lin WL, DeJesus-Hernandez M, et al. Unconventional translation of *C9ORF72* GGGGCC expansion generates insoluble polypeptides specific to c9FTD/ALS. *Neuron* 2013; 77: 639-646.
13. Mori K, Weng SM, Arzberger T, May S, Rentzsch K, Kremmer E, et al. The *C9orf72* GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTL/ALS. *Science* 2013; 339: 1335-1338.

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