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EDITORIAL

The *C9ORF72* mutation brings more answers and more questions

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Abstract

The clinical, neuropsychiatric and neuroimaging features of patients who carry the important new *C9ORF72* mutation are discussed in this special series of *Alzheimer's Research & Therapy*. First reported in November 2011, the *C9ORF72* mutation is the most common mutation associated with both frontotemporal dementia and amyotrophic lateral sclerosis in the Western hemisphere and Europe. It is a gene with strong penetrance, and the vast majority of subjects with the *C9ORF72* mutation die from a neurodegenerative condition. The most common clinical manifestation of disease in gene carriers is behavioral variant frontotemporal dementia. An extremely long hexanucleotide repeat (usually greater than 400), appears to lead to ribonucleic acid aggregates within the nucleus and suppression of gene expression. Finding therapies for *C9ORF72* will be difficult and require novel therapeutic approaches that involve suppression of the expression of the *C9ORF72* repeat.

Alzheimer's Research & Therapy has published a series of articles written about the important new *C9ORF72* mutation associated with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The clinical, neuropsychiatric and neuroimaging features of the patients who carry this mutation are discussed in this special series.

First reported in November 2011 [1,2], the *C9ORF72* mutation is the most common mutation associated with both FTD and ALS in the Western hemisphere and Europe (less is known about *C9ORF72* in Asia and Africa). At the University of California, San Francisco (UCSF), the chromosome 9 (C9) expansion accounts for 53% of all familial ALS, FTD and ALS/FTD cases referred to the center, more common than all of the other FTD and AD mutations together. The Mayo Clinic found *C9ORF72* expansions accounted for 12% of familial FTD and 24% of familial ALS patients from a sequential series of their patients. They also reported a 62% frequency in a University of British Columbia cohort of pathologically confirmed frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) probands [1]. In Finland, the expansion accounts for 46% of familial ALS and 21% of sporadic ALS, while it accounts for 33% of familial ALS cases in people of European descent [2]. It is a gene with strong penetrance, and the vast majority of subjects with the C9 expansion die from a neurodegenerative condition. While some subjects with this mutation develop FTD-spectrum disorders, others exhibit ALS, while still others have a mixture of both FTD and ALS at the time of clinical presentation. The mutation brings up important questions regarding selective vulnerability and why one member of a family gets ALS while another dies from FTD that remain unanswered.

The most common clinical manifestation of disease in gene carriers is behavioral variant frontotemporal dementia (bvFTD), and this mutation has its own unique anatomical features. Psychotic behaviors may suggest FTD due to *C9ORF72* versus other types of bvFTD, but distinguishing clinical symptoms still need to be defined into a clear phenotype. While the frontal lobe degeneration in C9-related FTD may be less severe than that in patients with sporadic bvFTD, some of the patients with the *C9ORF72* repeat appear to have more severe involvement of the thalamus [3,4] and cerebellum. How this degeneration intersects with the frontal involvement and modifies the clinical phenotype remains to be seen. Similarly, the neuropsychiatric prodrome of bvFTD and ALS in gene carriers needs to be better understood because early intervention will almost certainly be needed if effective therapies are going to be instituted.

C9 appears to mediate neurodegeneration via an RNA-mediated mechanism. The repeat is located on a non-coding region of *C9ORF72*, which encodes a protein with no known function that is expressed at high levels in the

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brain. The extremely long hexanucleotide repeat (estimated to be 700 to 1,600 units) appears to lead to RNA aggregates within the nucleus and suppression of gene expression through aberrant RNA splicing. Two other conditions, myotonic dystrophy and fragile-X-tremor-ataxia, cause disease by a similar mechanism. A loss of C9ORF72 protein function is another possible mechanism of disease. Finding therapies for *C9ORF72* will be difficult and require novel therapeutic approaches that involve suppression of the expression of the C9 repeat. Accurate animal models and well-characterized patient cohorts will be essential to understanding the underlying mechanisms of the disease pathway and the discovery of potential therapeutic targets. Such efforts are underway in myotonic dystrophy and will soon be applied to the C9 mutation.

This special series of *Alzheimer's Research & Therapy* expands our knowledge of *C9ORF72* with articles on its clinical [5,6], imaging [7], genetic counseling [8] and treatment aspects [9]. Clinical tests are available to screen for *C9ORF72* expansions, but refining the clinical phenotype and imaging markers will help clarify when such testing is recommended. Genetic counseling is a critical service to help patients and families to decide when to test for the expansion, whether or not to learn the results and how to interpret the results. Both FTD and ALS [10] are described in this special series. The risk of *C9ORF72* for FTD and ALS brings a new understanding to both disorders and brings us closer to the day when these diseases can be treated.

This article is part of a series on *The new FTD mutation on chromosome 9*, edited by Bruce Miller. Other articles in this series can be found at http://alzres.com/series/FTDmutation

Abbreviations

ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; C9, chromosome 9; C9ORF72, chromosome 9, open reading frame 72; FTD, frontotemporal dementia.

Competing interests

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