

C9orf72 Repeat Expansions in Rapid Eye Movement Sleep Disorder

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The chromosome 9 open reading frame 72 (*C9orf72*) gene, first identified in 2011, is located on chromosome 9p21 and encodes 11 exons. In normal individuals, two isoforms of *C9orf72* (isoforms a and b) are expressed in many regions of the human body, including the kidney, liver, testes, heart, and brain. The protein is found in high concentrations in many parts of the central nervous system, especially in the frontal cortex; it is largely found in the cytoplasm of neurons. The function of the *C9orf72* protein is unknown; however, it is postulated to play a role in membrane trafficking.

A GGGGCC hexanucleotide repeat is located in this gene in the first intron between the noncoding exons 1a and 1b, with a normal range between two and 23 repeats. Repeats greater than 30 are considered to be pathogenic. Research has demonstrated that this repeat expansion is the most common cause of familial amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD) among the Caucasian population and is inherited in an autosomal dominant pattern.¹ The clinical phenotype of patients with repeats between 23 to 30 is still not certain because this size has been found both in “normal” controls and in patients presenting with neurodegenerative diseases.² As characteristic for other repeat disorders, it is entirely possible that repeats in this range may have variable penetrance.

The mechanism by which *C9orf72* expansion causes disease is unknown but several hypotheses exist, including loss of *C9orf72* protein function or two independent gain-of-function theories.³ Evidence for disease pathogenicity from the loss of *C9orf72* function derives from the observation that low levels of *C9orf72* transcripts exist in expansion patients. This decrease in transcript is expected to affect membrane trafficking because *C9orf72* is thought to play a role in protein degradation. Two gain-of-function models include the cellular toxicity created from either the accumulation of RNA foci that sequester other RNA-binding proteins and/or the accumulation of dipeptide repeat proteins that are generated from a novel ATG-independent mechanism. Of course, it is also possible that disease pathogenesis could be due to the combined effect of all three pathways.

The *C9orf72* expansion accounts for 25% of familial FTLD cases worldwide; 6% of sporadic cases have been shown to have the mutation. There is a wide variation among populations, with the mutation being most common in Caucasians. The most common FTLD phenotype associated with *C9orf72* mutation is behavioral variant FTLD. These patients present with hallucinations, psychosis, and delusions with associated dementia. Progressive nonfluent aphasia is the next most common phenotype seen; semantic dementia phenotype is rarely associated with *C9orf72* mutations. Patients with *C9orf72* mutations show an earlier age of onset, with prominent frontal atrophy on neuroimaging.

In familial ALS, the worldwide incidence of *C9orf72* expansions is 34% and occur more frequently than SOD1 mutations. Similar to familial FTLD, a wide variation in the incidence of

C9orf72 expansions is noted among populations. Low frequencies are seen in progressive muscular atrophy and primary lateral sclerosis. ALS patients with *C9orf72* mutations present with an earlier age of onset, predominant bulbar symptoms, rapid progression, and associated cognitive and behavioral changes and have reduced survival rates.

The range of *C9orf72*-related disorders has widened since first described. They have been found in multiple cases of Huntington disease–like syndromes and one case each has been described in atypical Parkinson syndrome and multiple system atrophy (MSA). No expansions have been found in typical cases of progressive supranuclear palsy or corticobasal syndrome. Additionally, *C9orf72* expansions were detected in a small number of multiple sclerosis patients who subsequently developed ALS. Expansions have been found in low frequency in Alzheimer disease (less than 1%) and in one case each with dementia with Lewy body disease (DLBD) and sporadic Creutzfeldt-Jakob disease. No expansions have been detected in patients with hereditary spastic paraparesis.

The article in this issue by Daoud et al expands our knowledge of *C9orf72*-associated diseases by analysis of rapid eye movement (REM) sleep disorder.⁴ REM sleep is a complex state characterized by rapid eye movements, muscle atonia, and desynchronized electroencephalogram activity, when dreams occur. Several anatomic structures are involved, including the midbrain, brainstem, locus ceruleus, periaqueductal gray matter, hypothalamus, amygdala, and neocortex. Recent evidence suggests that GABAergic and glutamatergic neurotransmitters are involved in REM sleep. Because the pontine tegmentum and medial medulla are critical areas for muscle atonia, lesions in these areas abolish muscle atonia and induce REM sleep behavior. The amygdala with its connections to the brain stem nuclei regulates muscle tone and modulates the emotional aspect of sleep.⁵

REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behaviors with abnormal phasic or tonic electromyographic activity during REM sleep. The clinical phenotype of RBD is diverse and can vary from mild to severe. RBD may be idiopathic or secondary to a variety of disorders such as structural lesions (e.g. stroke, tumor, demyelination), neurodegenerative diseases, limbic encephalitis, fatal familial insomnia, narcolepsy, and medications (antidepressants, beta-blockers). RBD often predates the clinical presentation of several neurodegenerative disorders with a strong association with Parkinson disease, MSA, and DLBD. The prevalence of RBD is 90% to 100% in MSA, 15% to 58% in Parkinson disease, and 50% to 83% in DLBD. Sixty percent of patients with parkin mutations have RBD. Studies in other neurodegenerative diseases such as Alzheimer disease, progressive supranuclear palsy, Huntington disease, and spinocerebellar ataxias have also shown to exhibit RBD although in lower frequencies.⁶

In their study analyzing *C9orf72* repeat expansions in RBD, Daoud et al, rather than characterizing *C9orf72* repeat expansions in patients with a cohort of one particular disease, have analyzed it in patients with RBD.⁴ In this cohort of 344 patients with RBD, two carriers with *C9orf72* expansions were detected. On further analysis, both of these patients shared the same common haplotype that is observed in other populations, suggestive of a single founder mutation. It is interesting that both of these patients developed signs of parkinsonism. One patient likely had idiopathic Parkinson disease, whereas the other had features of parkinsonism but the clinical phenotype was not clearly characterized. Although *C9orf72* expansions have not been identified as a major cause in Parkinson disease, a small number of cases have been described having *C9orf72* expansions and parkinsonism. Because pathological data are not available, it is difficult to say whether both of these patients have evidence of synucleinopathy or another neurodegenerative process. However, in a clinicopathological study of *C9orf72* expansions, parkinsonism, and Parkinson disease, Cooper-Knock et al found only one patient with *C9orf72* expansion showing evidence of α -synucleinopathy.⁷ Until the pathogenesis of *C9orf72* disease is fully understood, it remains impossible to exclude *C9orf72* expansions as a rare cause of α -synucleinopathies and RBD.

The unknown pathophysiology of *C9orf72* expansions emphasizes the importance of careful disease phenotyping. The finding of *C9orf72* expansions in some patients with RBD expands the clinical presentation of *C9orf72*-mediated disease and may assist with elucidation of the mechanism of pathogenesis for *C9orf72*.

Anil Venkitachalam, Stacy Hume
Department of Medicine (Neurology), University of Alberta,
Edmonton

Oksana Suchowersky
Department of Medicine (Neurology), Department of Medical
Genetics, University of Alberta, Edmonton
Email: Oksana.Suchowersky@albertahealthservices.ca

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