

These violent repeats have violent extends

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease that causes paralysis and death typically within 3 years of onset. The rapidly progressive loss of motor neurons in the brain and spinal cord leads to muscle atrophy, causing weakness, muscle fasciculations, and spasticity. This interferes with normal movement, gait, speech, and swallowing. ALS progresses inexorably, causing paralysis and eventually death. There is currently no cure for ALS and only 2 drugs have been approved, but these only offer limited benefit. More effective therapeutic strategies are desperately needed.

Most ALS cases are sporadic, but around 10% have a family history. Although these familial cases are rarer than the sporadic ones, they have played an outsize role in contributing to insight into the causes and mechanisms of ALS. This is because these familial cases can be analyzed by genetic approaches to map and sequence genes that cause ALS. The first gene associated with familial ALS was *SOD1*.¹ *SOD1* mutations have been found in approximately 20% of familial cases, which equals approximately 2% of all ALS cases. It is believed that the ALS-causing mutations in *SOD1* lead to a toxic gain of function of the protein. Clinical trials in human patients with ALS are currently under way to test the efficacy of an *SOD1*-lowering therapy, using antisense oligonucleotides.² Although *SOD1* mutations in ALS are relatively rare, the path from *SOD1* gene discovery to targeted therapy illustrates the power of genetics in illuminating the causes of ALS, paving the path for the development of novel therapies. Owing to the explosion in new gene sequencing technologies, the number of ALS genes has been increasing exponentially¹—each new gene offering the hope for a better understanding of ALS mechanisms. The identification of causative genes for ALS will also improve early diagnosis, which will undoubtedly give therapies a better shot at success.

One of these newly discovered genes is now the most common genetic cause of ALS. Discovered in 2011, mutations in the *C9ORF72* gene cause ~40% of familial ALS cases and ~10% of sporadic cases.¹ The ALS-causing mutation in *C9ORF72* is a hexanucleotide repeat expansion located in a noncoding portion of the gene. Normally, the gene harbors only a handful of GGGGCC repeats, but in individuals with *C9ORF72* mutations, the number of repeats increases to hundreds or even thousands. Intense research efforts are under way to define how these violent nucleotide repeat expansions in *C9ORF72* cause ALS and to devise therapeutic strategies. Of interest, the repeat expansion in *C9ORF72* can be traced back to a single founding event, probably in Northern Europe.³ Despite being common in Europe and North America, it is extremely rare in Asian ALS populations.⁴ The paucity of *C9ORF72* mutations in Asia raises the question of whether repeat expansions in other genes could be more common causes of ALS in this population.

Beyond *C9ORF72*, repeat expansions in at least 2 other genes, *NOP56* and *ATXN2*, have been associated with motor neuron disease, including ALS.^{5,6} Noncoding GGCCTG-repeat expansions in the *NOP56* gene cause spinocerebellar ataxia type 36, which can present with prominent motor neuron degeneration. Long trinucleotide CAG-repeat expansions in the *ATXN2* gene cause spinocerebellar ataxia type 2 (SCA2). Of interest, intermediate-length CAG repeat expansions in the same gene are associated with ALS.⁶ Therapeutic strategies to target *ATXN2* are being pursued for SCA2 and ALS.^{7,8}

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In this issue of *Neurology® Genetics*, Hirano et al.⁹ analyzed the length of the repeat expansion in 3 genes, *ATXN8OS*, *C9ORF72* and *NOP56*, in 103 Japanese patients with ALS. In this cohort, 3 patients harbored a pathologic expansion in the *ATXN8OS* gene. Although healthy controls harbored between 15 and 50 CTA/CTG repeats, patients with ALS had more than 80 repeats. Since the authors found *ATXN8OS* repeat expansions in 3% of patients with ALS, it suggests that such mutations may be relatively common in Japan.

Nucleotide repeat expansions in *ATXN8OS* have been previously connected with another neurodegenerative disease, spinocerebellar ataxia type 8 (SCA8). SCA8 is a slowly progressive ataxia with disease onset from age 1 to the early 70s but typically with an adult onset.¹⁰ As opposed to the rapid progression observed in ALS, SCA8 progression is slow and spans decades, regardless of the initial age at onset; lifespan is typically not shortened. Initial symptoms are scanning dysarthria with a characteristic drawn-out slowness of speech and gait instability. Various atypical clinical features have also been identified in patients carrying an *ATXN8OS* expansion, such as parkinsonism, multiple-system atrophy, severe childhood onset, oromandibular dystonia, dysphagia, respiratory muscle weakness, or seizure-like episodes.

The next steps are to extend the analysis of *ATXN8OS* in a larger Japanese ALS population to confirm these exciting findings and to also test other Asian ALS patient populations (e.g., China and Korea). It will also be important to carefully re-evaluate SCA8 cases and pedigrees to define the prevalence of symptoms warranting a diagnosis of ALS. Looking to the mechanism, future studies should focus on how the *ATXN8OS* repeat expansions cause pathologies and how such pathologies contribute to motor neuron degeneration.

The work of Hirano et al. is especially interesting in a clinical diagnostic standpoint. We now see a significant genetic overlap between neurodegenerative diseases such as spinocerebellar

ataxia, hereditary spastic paraplegia, ALS, and frontotemporal dementia. It is still unclear whether the clinical manifestations of these mutations result from different pathologic mechanisms, different affected cell types, or different genetic backgrounds harboring a diverse set of genetic modifier genes. It may be beneficial to start developing and implementing broad multigene test panels for neurodegenerative and neuromuscular diseases, as is standard practice in cancer screening.

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