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Amyotrophic lateral sclerosis (ALS) is usually sporadic, but 5%–10% of patients have a hereditary form of the disease. About 20% of familial patients have mutations in the *SOD1* gene,[1] and recently other gene mutations have been found in familial ALS: *TDP-43*, *FUS,* and *VCP*.[2–5] Interestingly, the protein products of 2 of these genes, TDP-43 and FUS, are likely involved in RNA metabolism. TDP-43 forms cytoplasmic inclusions in neurons of patients with both sporadic and familial ALS and frontotemporal dementia.

Genetic risk factors may play a role in sporadic as well as familial ALS, but the results of association studies have been mixed. For example, the gene for the neurotrophic factor VEGF is a possible risk factor in various European populations,[6] but studies in other populations did not confirm the finding.[7] It is now clear that there is no genetic risk factor for ALS as strong as *APOE* is for Alzheimer disease, and finding and confirming weaker risk factors requires large studies in multiple populations with well-matched controls.

Several months ago, Elden and colleagues[8] reported a novel risk factor for ALS in *ATXN2*, the gene for the polyglutamine expansion neurodegenerative disease spinocerebellar ataxia 2 (SCA2). This gene showed up in a screen for modifiers of TDP-43 toxicity in yeast and has a similar effect in *Drosophila*.[8] TDP-43 and ataxin 2 interact in an RNA-dependent manner. Perhaps most importantly for the human disease connection, more than twice as many patients with ALS as controls had ataxin 2 polyglutamine repeat lengths in the high normal range (≥24 glutamines). The ratio was even greater with repeat lengths ≥27 glutamines, close to the range associated with SCA2 (≥33). If confirmed, this would mean that *ATXN2* is the most common genetic risk factor for ALS identified to date.

In the current issue of *Neurology*®, Van Damme and colleagues[9] extend the analysis of *ATXN2* to a larger cohort of Dutch and Belgian patients with ALS and controls. The results support the previously reported American findings, with an interesting twist. The association of ALS with *ATXN2* was only found with longer repeat lengths (≥29), and it was found in familial as well as sporadic ALS. The disease manifestations in patients with long *ATXN2* repeats ranged from typical, rapidly progressive ALS to a disorder with earlier onset, slower progression, and sensory involvement. In at least some of these patients, there is clinical overlap between ALS and SCA2, i.e., SCA2 may be presenting as a motor neuron disease with features of ALS, as has been reported previously.[10] Such clinical overlap has been reported previously between SCA2 and Parkinson disease,[11] and between ALS and spinal and bulbar muscular atrophy (SBMA, Kennedy disease).[12] Many patients with SBMA are initially diagnosed with ALS because both disorders cause progressive weakness due to motor neuron degeneration, although the disease course and other clinical features are generally different.

Could the apparent increase in risk of ALS with long *ATXN2* repeats be simply due to the misclassification of SCA2 as ALS? Van Damme et al. argue not for various reasons, including the presence of long *ATXN2* repeats in patients with sporadic ALS with a typical disease presentation and the observation that SCA2 can present with a pure motor neuron degeneration phenotype.[9] However, neither study found an association of ALS with *ATXN2* repeat length overall, only at the longer end of the repeat range[8,9]; this may explain why this locus has not appeared in genome-wide association studies of ALS.[13] Also, increased instability of the repeat might make it difficult to detect this association even with directly adjacent genetic markers. Further studies in well-characterized ALS populations with well-matched controls should help to settle whether *ATXN2* repeat length is truly a risk factor for ALS. A study by Lee and colleagues[14] in the current issue of *Neurology*® did not find an association of ALS with long repeats in other polyglutamine disease genes (the SBMA gene was not included).

See pages 2062 and 2066

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Association studies with genes containing multiple variants are challenging. Given the range of different repeat lengths in the *ATXN2* gene, the authors tried to circumvent this problem by defining repeat classes. As this was done post hoc in both articles, stringent significance testing may be difficult to apply. As both groups apply different cutoffs to construct repeat classes, the association data remain inconclusive.

Despite these potential shortcomings, both studies demonstrate that expansion of the *ATXN2* repeat to pathologic sizes of ≥32 can be associated with a clinical phenotype dominated by motor neuron disease. Van Damme and coworkers point out that appearance of cerebellar dysfunction in these patients can be delayed by up to 2 decades.

It remains unknown why pathologic expansion of ≥32 repeats in the *ATXN2* gene most commonly leads to cerebellar degeneration, but to a Parkinson disease or ALS-like phenotype in occasional individuals. Environmental or genetic factors can affect the phenotype of neurodegenerative diseases. The cluster of ALS-like manifestations in 2 pedigrees is consistent with effects of genetic background and perhaps genetic variants within or close to the *ATXN2* gene. The presence of interruptions in the expanded repeat has been suggested as a cause of the Parkinson-like phenotype seen with *ATXN2* mutations.[15]

The take-home lesson for neurologists is to be aware that ALS and SCA2 can have partially overlapping clinical features. Accurate diagnosis has important implications for a patient's prognosis and the risk to family members. The overlap in clinical manifestations also indicates an overlap in the disease mechanisms, with common features of toxic proteins prone to aggregation, mislocalization, and aberrant interactions that ultimately lead to motor neuron dysfunction and death. And an overlap in the mechanisms suggests that a common approach to treatment may be successful.

DISCLOSURE

Dr. Fischbeck serves on scientific advisory boards for and received funding for travel from Biogen Idec, Prosensa, Kennedy's Disease Association, SMA Foundation, Hereditary Disease Foundation, TREAT-NMD, and Association Française contre les Myopathies and receives research support from the NIH/NINDS. Dr. Pulst serves on the editorial boards of *Journal of Cerebellum*, *NeuroMolecular Medicine*, *CONTINUUM*, *Experimental Neurology*, *Neurogenetics*, *Nature Clinical Practice Neurology*, and as Editor-in-Chief for *Current Genomics*; is listed as author on patents re: Nucleic acids encoding ataxin-2 binding proteins, Nucleic acid encoding Schwannomin-binding-proteins and products related thereto, Transgenic mouse expressing a polynucleotide encoding a human ataxin-2 polypeptide, Methods of detecting spinocerebellar ataxia-2 nucleic acids, Nucleic acid encoding spinocerebellar ataxia-2 and products related thereto, Schwannomin-binding-proteins, and Compositions and methods for spinocerebellar ataxia; receives publishing royalties for *The Ataxias* (Churchill Livingston, 2007), *Genetics in Neurology* (ANN Press, 2005), *Genetics of Movement Disorders* (Academic Press, 2003), *Neurogenetics* (Oxford University Press, 2000), and *Molecular Genetic Testing in Neurology, 2nd–5th* (AAN Press, 1996); serves on the speakers' bureau for Athena Diagnostics, Inc.; receives research support from the NIH/NINDS; and has received license fee payments from Cedars-Sinai Medical Center.

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