

Does Somatic Mosaicism Account for Some Sporadic ALS?

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Amyotrophic lateral sclerosis (ALS) is characterized by degeneration of motor neurons in the brain, brainstem, and spinal cord, resulting in muscle atrophy and weakness. Progression of the disease eventually leads to respiratory failure and death, usually within 3–5 years of symptom onset. Most ALS cases are sporadic, with approximately 5%–10% being familial.¹ To date, mutations in more than 120 genes have been shown to cause or increase the risk of ALS (alsod.ac.uk), with mutations in about 20 genes being linked to monogenic forms of ALS. It is estimated that 40%–60% of individuals with familial ALS have an identified genetic mutation, depending on the population studied. The causes of the other familial ALS and more than 90% of sporadic ALS cases remain unknown.²

In this issue of *Neurology® Genetics*, Hisahara et al.³ provide genetic evidence of somatic mosaicism of a novel *FUS* frameshift mutation in an ALS patient (case 1), who transmitted the mutant *FUS* to her heterozygous and affected son (case 2). The age at onset in case 1 is reported as 44 years of age with invasive ventilation marking disease end point 6 years later. However, case 2 showed a much earlier disease onset around 11 years of age and a rapid disease progression, requiring invasive ventilation less than 2 years after disease onset. Whole exome sequencing (WES) analysis of the DNA isolated from a blood sample of case 2 revealed a novel heterozygous 4 nucleotide deletion in *FUS* (c.1542_1545delGGGT, p.Gly515Serfs13*). The clinical features of case 2 are consistent with *FUS* mutations of this type because patients with a truncated *FUS* protein without a C-terminal nuclear localization signal generally show an early onset and rapid progression of disease.

It seemed reasonable to expect that the *FUS* mutation in case 2 was inherited from his mother (case 1). However, the mutation was not as readily detected in the WES data using DNA isolated from a blood sample of case 1. Detailed analysis revealed a single read with this mutation among a total of 30 reads, suggesting somatic mosaicism of this mutant *FUS* allele at a low frequency in the mesoderm-derived white blood cells of case 1. The authors subsequently performed deep targeted next generation sequencing of DNA isolated from blood and saliva of case 1 and validated a similar low-read frequency (<2%) of this mutation. Semiquantitative analysis of the mutant allele abundance using Sanger sequencing of DNA isolated from blood, saliva, hair, and nail of case 1 showed varying levels of the mutant allele across different cell types. Although not fully quantified, the mutant allele frequency seemed to be much higher in the DNA samples isolated from ectoderm-derived hair and nail, which share their germ layer origin with the nervous system. Combined, these data lead the authors to propose that case 1 exhibits somatic mosaicism of this *FUS* mutation.

Somatic mutations, arising in early embryonic development and leading to mosaicism, have emerged as pathogenic drivers for neurodevelopmental and neurodegenerative disorders.^{4,5} Although these mutations may be absent or undetectable in DNA isolated from peripheral blood, they might be present in subsets of neurons and glia in the CNS, driving diverse clinical outcomes. The much milder clinical phenotype in case 1 might be explained by mosaicism of this mutation in her CNS.

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Without case 2, it is quite likely that case 1 would have been diagnosed as a sporadic ALS patient without any known genetic causes, even if a standard WES or ALS/frontotemporal dementia genetic panel test had been performed using DNA isolated from peripheral blood. The findings by Hisahara et al. raise the possibility that somatic mosaicism, although rare, may account for some sporadic ALS cases. Their findings also raise at least 2 significant issues regarding the identification of somatic mosaicism in ALS research and clinical practice.

First, sequencing strategies need to be considered. Sanger sequencing is limited in its ability to detect somatic mosaicism with a minimum detection threshold of ~15% for the mutant allele. Allele frequencies below this threshold are difficult to distinguish from background noise. Currently, standard WES is designed to detect heterozygous variants in monogenic disorders, with a depth of coverage of ~100× or less. The presence of single or limited reads of a variant allele makes a genetic diagnosis quite challenging, especially when taking low sequencing quality at some loci into consideration. Therefore, higher depth of coverage of WES or similar approaches may be necessary when considering somatic mosaicism. Droplet digital PCR-sequencing may provide much higher detection sensitivity (~0.001%) for the detection or validation of somatic mutations.

Second, the origins of the DNA sample need to be considered. It seems that this novel *FUS* mutation arose during early embryonic development before gastrulation in case 1. Most DNA samples to be sequenced are isolated from peripheral white blood cells, which are derived from mesoderm. Their mutant allele frequency may be significantly different than that in the ectoderm-derived nervous system, as shown in case 1. DNA samples isolated from easily accessible ectodermal tissues, such as hair and nail, should be considered for genetic analysis when somatic mosaicism is suspected.

Identification of somatic mosaicism remains a significant challenge. However, it may provide a rare opportunity to elucidate the pathogenesis of ALS. For example, ALS typically manifests locally and spreads to neighboring regions, but the mechanism underlying such a spread is largely unclear. Investigating whether degeneration of some neurons with a mutation could spark degeneration in neighboring neurons with or without the mutation may establish a mechanistic framework for understanding disease progression. Further studies may be directed to characterize brain and spinal cord autopsy samples from patients with somatic mosaicism using comprehensive genetic, biochemical and pathologic approaches, such as single cell “multi-omics.” Although technically challenging, these studies may yield crucial information to help better understand the pathogenesis of ALS, as well as other neurodegenerative disorders, and to provide a rational basis for therapeutic interventions.

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Disclosure

The authors declare no competing financial interests. Go to Neurology.org/NG for full disclosures.

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