New clinical trial takes personalized approach for rare type of ALS in Appalachia

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Members of the multidisciplinary team at UK HealthCare's ALS Clinic which has been named a Certified Treatment Center of Excellence by the ALS Association. Credit: University of Kentucky

ALS, or amyotrophic lateral sclerosis, is a neurodegenerative disease of some fame in the United States. Many Americans know the illness,

which currently has no cure, as Lou Gehrig's disease, after the beloved baseball player whose career and life were cut short by the condition in the 1930s and 1940s.

More recently, renowned physicist Stephen Hawking died of ALS. Perhaps more than anyone else, Hawking reminds us of the particular cruelty of the disease, which slowly robs a person of muscle movement while leaving their cognitive abilities intact. The average life expectancy after diagnosis is only four to five years and nearly everyone with ALS ultimately dies from the inability to breathe.

Around 6,000 new cases of ALS are diagnosed annually, making it the most common motor neuron disease in the U.S. About 90 percent of cases are sporadic—without genetic cause—but the remaining 10 percent of cases are familial, caused by a genetic variant passed down from parent to child. It was only in the 1990s that researchers first identified a gene involved in familial ALS—the SOD1 gene, which still appears to be the most common genetic variant in the U.S. and western Europe. More than 16 other genetic variants have since been identified, sometimes with specific regional distributions.

At the University of Kentucky, a multidisciplinary team of clinicians and scientists is investigating a therapy for one particular genetic type of ALS that seems to be clustered in central Appalachia. Dr. Edward Kasarskis, director of UK's ALS Multidisciplinary Clinic, discovered the phenomenon by chance, when two ALS patients with the same last name and hometown came into his clinic—15 years apart. Not long after he treated the second patient, her son showed up in his clinic with ALS. Over time, as Kasarskis saw more ALS patients from the same geographic areas—which he was familiar with because of his love of hiking—he started to suspect that something genetic might be at play.

"The discovery owes credit, at least partially, to attention to maps and

backpacking," Kasarskis said. "And if you weren't treating patients in the same place over a long period of time, you wouldn't notice these patterns."

Kasarksis came to discover a trend of ALS cases caused by a mutation in the FUS gene, which regulates MnSOD, the major antioxidant defense enzyme located in the mitochondria of motor neuron cells. People with this specific FUS mutation don't have enough of the MnSOD enzyme, which means their motor neurons in the spinal cord break down from oxidative stress and become unable to carry messages from the brain to the muscles.

Investigation into public records allowed Kasarskis' research team to trace the extended family with FUS-related ALS case back to Lee County, Virginia, in the 1800s. Strangely, the public records, which also identify descendants and relatives of people known to have ALS, have sometimes aided in diagnosis. More than once, an ALS patient has shown up in Kasarskis' clinic, and he's recognized their name from genealogy records, allowing him to facilitate a precise genetic diagnosis.

"There are really so few of these patients—it's unique in our region. Now I ask all my ALS patients if their ancestors came from this part of Virginia," he said. He's also spent extended time meeting with communities in the region, providing ALS education and collecting DNA samples.

As a clinician and a scientist, Kasarskis recognized that studying ALS through this particular genetic mutation would allow for robust and tightly controlled laboratory study, including the use of animal models and pluripotent stem cells differentiated into motor neurons. To conduct such research, he teamed up with two other UK scientists, Daret St. Clair, Ph.D., professor of toxicology and cancer biology and associate director of basic science for the UK Markey Cancer Center, and Haining

Zhu, Ph.D., professor of molecular and cellular biochemistry, to investigate a targeted approach to this particular type of ALS. Together, they are leading the TRANSLATE study (Treatment of FUS-related ALS with Betamethasone), which explores whether the FDA-approved drug betamethasone can increase the MnSOD enzyme that protects against oxidative stress in patients with FUS-related ALS. The research team also includes experts in pharmacology, physical therapy, and nursing.

"This clinical trial involves several labs and types of expertise – it's ultra-collaborative. But our clinic is also collaborative and multidisciplinary. It's the kind of care these patients need, so it flows naturally into the research questions," Kasarskis said.

The collaboration between Kasarskis and St. Clair precedes the TRANSLATE study, and also began through a stroke of coincidence. While the FUS gene was identified as a cause of familial ALS in 2009, St. Clair's work had already demonstrated the FUS protein was involved with the MnSOD enzyme, though she hadn't connected it to ALS. The TRANSLATE study, which is supported by the UK Multidisciplinary Value Program, had its roots in this collaboration. The team screened hundreds of FDA-approved drugs that could potentially increase the antioxidant capacity of cells. The screening process stemmed from a project in St. Clair's lab at the Markey Cancer Center, where she was trying to find drugs that were nontoxic and whose antioxidant properties could reduce side-effects of cancer therapy.

"During the screening process, we found that one of these drugs being used extensively is betamethasone. It's used in all kinds of inflammatory diseases, it's very non-toxic so you can give short-term, high doses without problems for patients, and it has a long history of use for other conditions. And that's how the TRANSLATE clinical trial began," St. Clair said.

In the trial, participants with FUS-related ALS are given doses of betamethasone via injection, and then blood and antioxidant measurements are taken to see if the intended effect has been achieved. The research team is hoping to enroll ten participants who have active FUS-related ALS or are carriers. Then, after proving the research concept, the team will determine if this approach could benefit patients with other types of ALS.

"We think that this benefit may not be limited to this particularly focused group of ALS patients, but that it could also be applicable in the larger ALS population, which has a similar component of mitochondria damage from oxidative stress," St. Clair said.

Provided by University of Kentucky